ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 3 | Volume: 19 | Year: 2023

MEDICAL JOURNAL OF BAKIRKÖY

www.bakirkoytip.org

ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 3 | Volume: 19 | Year: 2023

MEDICAL JOURNAL OF BAKIRKÖY

Medical Journal of Bakırköy of is an official scientific Journal of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (BMJ)
It is published quarterly as 4 issues every year (March, June, September, December).
Medical Journal of Bakirköy is an open Access, free and peer-reviewed journal and indexed in ESCI, EMBASE, Scopus, EBSCO and ULAKBİM TR Dizin.
Instructions for Authors and publication policy is available on our website.
www.bakirkoytip.org

galenos yayınevi

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
GSM: +90 530 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Printing Date: September 2023
ISSN: 1305-9319 **E-ISSN:** 1305-9327
International scientific journal published quarterly.

Advisory Board

Advisory Board

Advisory Board

Advisory Board

About Us

Journal History

The Medical Journal of Bakırköy is the official scientific journal of the Dr. Sadi Konuk Training and Research Hospital. It covers subjects on general medicine, published only in English, and is independent, open-access, peer-reviewed periodical published quarterly in March, June, September and December since 2005.

Title: Medical Journal of Bakırköy

Journal Abbreviation: Med J Bakirkoy

ISSN: 1305-9319

E-ISSN: 1305-9327

Free-of-Charge Publication

No fee is charged from the authors during the submission, evaluation and publication process. Journal practices, ethical rules, technical information and necessary forms are specified on the journal's web page.

The manuscripts must be submitted via the Manuscript Manager online article system, represented on the journal website.

Abstracting and Indexing

Web of Science – Emerging Sources Citation Index

TUBITAK ULAKBIM TR Index

Scopus

EBSCO – Academic Search Complete

J-Gate

Embase

CINAHL Complete

ScopeMed

WorldCat

Infobase

Ulrich's Database

Ideal Online

Türkiye Atıf Dizini

Türk Medline

Copyright

The authors agree to transfer the copyright to the Dr. Sadi Konuk Training and Research Hospital when the article is accepted for publication.

The Medical Journal of Bakırköy is an open access publication, and the journal's publication model is based on Budapest Open Access Initiative (BOAI) declaration. All published content is available online and free of charge at bakirkoymedj.org. The journal's content is licensed under a Creative Commons Attribution-NonCommercial (CC BY-NC-ND) 4.0 International License.

The copyright covers the exclusive and unlimited rights to reproduce and distribute the article in any form of reproduction (printing, electronic media or any other form); it also covers translation rights for all languages and countries.

After receiving and accept decision for publication, submissions must be accompanied by the "Copyright Transfer Statement". The form is available for download on the journal's manuscript submission and ealuation site. The copyright transfer form should be signed by all contributing authors and a scanned version of the wet signed document should be submitted.

Digital Archiving and Preservation Policy

Digital preservation is a set of processes and activities that ensure the retrieval and distribution of information now available in digital formats to guarantee long-term, perpetual access. The preservation policy includes the following measures:

Website Archiving

All of the electronic content (website, manuscript, etc.) is stored in three different sources. Content on a server is online and accessible to readers. A copy of the same content is preserved as a backup on other servers. Should a server fail, other resources can be brought online, and the website is expected to be available in 24-36 hours.

Abstracting/Indexing Services

Our journal's Abstracting/Indexing services store essential information about articles. In addition, some of Medical Journal of Bakırköy's Abstracting/Indexing services archive metadata about the article and electronic versions of the articles.In this way, copies of articles are presented to the scientific community through these systems as an alternative to journals.

Author Self-Archiving Policy

Authors are permitted and encouraged to post their articles on personal and institutional websites after publication (while providing full bibliographic details and a link to the original publication).

Advisory Board

The Medical Journal of Bakırköy aims to to publish original research papers of the highest scientific and clinic value on general medicine. Additionally, educational material reviews on basic developments, short editorial notes and case reports are published.

The Medical Journal of Bakırköy encourages and enables academicians, researchers, specialists and primary care physicians to publish their valuable research in all branches of medicine.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Author(s) and copyright owner(s) grant access to all users for the articles published in the The Medical Journal of Bakırköy as free of charge.

Open Access Policy is based on rules of Budapest Open Access Initiative (BOAI). By "open access" to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself.

All published content is available online, free of charge at bakirkoymedj.org.

Creative Commons

This Journal's content is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

CC BY-NC-ND: This license allows reusers to copy and distribute the material in any medium or format in unadapted form only, for non-commercial purposes only, and only so long as attribution is given to the creator.

CC BY-NC-ND includes the following elements:

BY – Credit must be given to the creator

NC – Only noncommercial uses of the work are permitted

ND – No derivatives or adaptations of the work are permitted

Advertising Policy

This journal's advertising sales and editorial processes are separated to ensure editorial independence and reduce the effects of financial interests.

Current or potential sponsors and advertisers do not affect editorial decisions in the journal. Advertisers and sponsors have no control or influence over the results of a user's website searches.

Advertisements should not be deceptive or misleading and must be verifiable. Excessive or exaggerated expressions does not be allowed.

If the text or image contains inappropriate or offensive content or is about personal, racial, ethnic, sexual orientation or religious content, these advertisements are not accepted.

Advertisers are responsible for ensuring that their advertisements comply with applicable laws regarding deceptive and/or offensive content and ethical issues.

Especially drug and medical product advertisements can be presented on the cover pages of the journal, separately from the published scientific content and without page number.

The published advertisements are pointed and distinguishable from the editorial content.

Material Disclaimer

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Dr. Sadi Konuk Training and Research Hospital, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

Permissions

Requests for permission to reproduce published material should be sent to the publisher.

Publisher: Galenos
Adress: Molla Gürani Mh. Kaçamak Sk. 21/1 Fındıkzade, Fatih, Istanbul, Türkiye
GSM: +90 530 177 30 97
Web page: http://www.galenos.com.tr
E-mail: info@galenos.com.tr

Ethical Policy

Peer-Review

Submission is considered on the conditions that papers are previously unpublished and are not offered simultaneously elsewhere; that authors have read and approved the content, and all authors have also declared all competing interests; and that the work complies with the ethical approval requirements and has been conducted under internationally accepted ethical standards. If ethical misconduct is suspected, the Editorial Board will act in accordance with the relevant international rules of publication ethics (i.e., COPE guidelines).

Editorial policies of the journal are conducted as stated in the rules recommended by the Council of Science Editors and reflected in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. Accordingly, authors, reviewers, and editors are expected to adhere to the best practice guidelines on ethical behavior contained in this statement.

Submitted manuscripts are subjected to double-blinded peer-review. The scientific board guiding the selection of the papers to be published in the journal consists of elected specialists of the journal and, if necessary, selected from national and international experts in the relevant field of research. All manuscripts are reviewed by the editor, section associate editors, and at least two external expert reviewers.

Human and Animal Rights

For the experimental, clinical, and drug human studies, approval by the ethical committee and a statement on the adherence of the study protocol to the international agreements (World Medical Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended October 2013) are required. In experimental animal studies, the authors should indicate that the procedures followed were by animal rights (Guide for the care and use of laboratory animals), and they should obtain animal ethics committee approval. The Ethics Committee approval document should be submitted to the Medical Journal of Bakırköy together with the manuscript.

The approval of the ethics committee; a statement on the adherence to international guidelines mentioned above; and proof that the patient's informed consent is obtained should be indicated in the `Material and Method` section. These items are required for case reports whenever data/media could reveal the identity of the patient.

For persons under 18 years of age, please provide a consent form that includes both parents' signatures or of the person's legal guardian or supervisor.

Plagiarism and Ethical Misconduct

The Medical Journal of Bakırköy uses plagiarism screening service to verify the originality of content submitted before publication.

Plagiarism: To republish whole or part of a content in another author›s publication without attribution.

Fabrication: To publish data and findings/results that do not exist.

Duplication: Using data from another publication; this includes republishing an article in different languages.

Salamisation: Creating multiple publications by abnormally splitting the results of a study.

Data Manipulation/Falsification: Manipulating or deliberately distorting research data to give a false impression.

We disapprove of such unethical practices and of efforts to influence the review process with such practices as gifting authorship, inappropriate acknowledgements, and references in line with the COPE flowcharts.

Submitted manuscripts are subjected to automatic software evaluation for plagiarism and duplicate publication. Authors are obliged to acknowledge if they published study results in whole or in part in the form of abstracts.

DUTIES OF PUBLISHER:

Handling of Unethical Publishing Behaviour

The publisher will take all appropriate measures to modify the article in question, in close cooperation with the editors, in cases of alleged or proven scientific misconduct, fraudulent publication, or plagiarism. This includes the prompt publication of an erratum, disclosure, or retraction of the affected work in the most severe case. Together with the editors, the publisher will take reasonable steps to detect and prevent the publication of articles in which research misconduct occurs and will under no circumstances promote or knowingly allow such abuse to occur.

Editorial Autonomy

The Medical Journal of Bakırköy is committed to ensuring the autonomy of editorial decisions without influence from commercial partners.

Intellectual Property and Copyright

The Medical Journal of Bakırköy protects the property

Advisory Board

and copyright of the articles published in the journal and maintains each article's published version of the record. The journal provides the integrity and transparency of each published article.

Scientific Misconduct

The Medical Journal of Bakırköy's publisher takes all appropriate measures regarding fraudulent publication or plagiarism.

DUTIES OF EDITORS:

Decision on Publication and Responsibility

The editor of the journal strives to meet the needs of readers and authors, and to provide a fair and appropriate peer-review process. The editor is also responsible for deciding which articles submitted to the journal should be published and guided by the policies subjected to legal requirements regarding libel, copyright infringement, and plagiarism. The editor might discuss such policies, procedures, and responsibilities with reviewers while making publication decisions. The editor is responsible for the contents and overall quality of the publication.

Objectivity

Articles that are submitted to the journal are always evaluated without any prejudice.

Confidentiality

The editor must not disclose any information about a submitted article to anyone other than editorial staff, reviewers, and publisher.

Conflicts of Interest and Disclosure

The Medical Journal of Bakırköy does not allow any conflicts of interest among authors, reviewers, and editors. Unpublished materials in a submitted article must not be used by anyone without the express written assent of the author.

Fundamental Errors in Published Works

Authors are obliged to notify the journal's editors or publisher immediately and to cooperate with them to correct or retract the article if significant errors or inaccuracies are detected in the published work. If the editors or publisher learn from a third party that a published work contains a material error or inaccuracy, the authors must promptly correct or retract the article or provide the journal editors with evidence of the accuracy of the article.

DUTIES OF REVIEWERS:

Evaluation

Reviewers evaluate manuscripts without regard for the origin, gender, sexual orientation, or political philosophy of the authors. Reviewers also ensure a fair, blind peer review of the submitted manuscripts for evaluation.

Confidentiality

All the information relative to submitted articles is kept confidential. The reviewers must not be discussed with others except if authorized by the editor.

Disclosure and Conflict of Interest

The reviewers have no conflicts of interest among authors, funders, editors, etc.

Contribution to editor

Reviewers help the editor make publishing decisions and may also assist the author in improving the manuscript.

Objectivity

Reviewers offer objective judgments and evaluations. The reviewers express their views clearly with appropriate supporting arguments.

Acknowledgement of Sources

Reviewers ought to identify a relevant published study that the authors have not cited. Reviewers also call to the editor's attention any substantial similarity or overlap between the manuscript and any other published paper of which they have personal knowledge.

DUTIES OF AUTHORS:

Reporting Standards

A submitted manuscript should be original, and the authors ensure that the manuscript has never been published previously. Research data should be represented literally in the article. A manuscript should include adequate detail and references to allow others to replicate the study.

Originality

Authors must ensure that their study is entirely original. References to the literature should be appropriately cited.

Multiple Publications

Authors should not submit the same study to multiple journals. Simultaneous submission of the same study to

Ethical Policy

more than one journal is unacceptable and constitutes unethical behaviour.

Acknowledgement of Sources

Acknowledgement to the work of others must be given. Authors should cite publications of relevance to their own study. All of the sources for the author's study should be noted.

Authorship of a Paper

Authorship of a paper ought to be limited to those who have made a noteworthy contribution to the study. If others have participated in the research, they should be listed as contributors. Authorship also includes a corresponding author who is in communication with the editor of a journal. The corresponding author should ensure that all appropriate co-authors are included in a paper.

We expect the corresponding author to indicate the institution where the study is carried out as the institution address.

Disclosure and Conflicts of Interest

All sources of financial support should be disclosed. All authors should disclose if a meaningful conflict of interest exists in the process of forming their study. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board of the The Medical Journal of Bakırköy. The ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors to disclose a potential conflict of interest. The journal's Editorial Board determines cases of a potential conflict of interest of the editors, authors, or reviewers within the scope of COPE and ICMJE guidelines.

Conditions that provide financial or personal benefit bring about a conflict of interest. The reliability of the scientific process and the published articles is directly related to the objective consideration of conflicts of interest during the planning, implementation, writing, evaluation, editing, and publication of scientific studies.

Financial relations are the most easily identified conflicts of interest, and it is inevitable that they will undermine the credibility of the journal, the authors, and the science. These conflicts can be caused by individual relations, academic competition, or intellectual approaches. The authors should refrain as much as possible from making agreements with sponsors in the opinion of gaining profit or any other advantage that restrict their ability to access all data of the study or analyze, interpret, prepare, and publish their articles. Editors should refrain from bringing together those who may have any relationship between them during the evaluation of the studies. The editors, who make the final decision about the articles, should not have any personal, professional, or financial ties with any of the issues they are going to decide. Authors should inform the editorial board concerning potential conflicts of interest to ensure that their articles will be evaluated within the framework of ethical principles through an independent assessment process.

If one of the editors is an author in any manuscript, the editor is excluded from the manuscript evaluation process or a guest editor is assigned instead. In order to prevent any conflict of interest, the article evaluation process is carried out as double-blinded. Because of the double-blinded evaluation process, except for the Editor-in-Chief, none of the editorial board members, international advisory board members, or reviewers is informed about the authors of the manuscript or institutions of the authors.

Our publication team works devotedly to ensure that the evaluation process is conducted impartially, considering all these situations.

Conflict of Interest

The declaration of the conflict of interest between authors, institutions, acknowledgement of any financial or material support, aid is mandatory for authors submitting a manuscript, and the statement should appear at the end of the manuscript. Reviewers are required to report if any potential conflict of interest exists between the reviewer and authors, institutions.

Appeals and Complaints

Appeal and complaint cases are handled within the scope of COPE guidelines by the Editorial Board of the journal. Appeals should be based on the scientific content of the manuscript. The final decision on the appeal and complaint is made by Editor-in-Chief.

Advisory Board

Advisory Board

Contents

Researches

Contents

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:236-241
DOI: 10.4274/BMJ.galenos.2023.2023.1-6

Research

Prognosis of Childhood Atopic Asthma: A 6-year Follow-up Study

Çocukluk Çağı Alerjik Astım Prognozu: 6 Yıllık Bir Klinik İzlem Çalışması

Semiha Bahçeci Erdem[1], Hikmet Tekin Nacaroğlu[2], Ömer Akçal[3]

[1]İzmir Bakırçay University Faculty of Medicine, Çiğli Training and Research Hospital, Department of Pediatric Allergy and Immunology, İzmir, Türkiye
[2]İstanbul Medipol University Faculty of Medicine Hospital, Department of Pediatric Immunology and Allergy Diseases, İstanbul, Türkiye
[3]İstanbul Biruni University Faculty of Medicine Hospital, Clinic of Pediatric Immunology and Allergy Diseases, İstanbul, Türkiye

ABSTRACT

Objective: There have been few studies on prognosis and factors influencing the prognosis in children with atopic asthma. We intended to evaluate the prognosis, clinical remission rate, and influencing factors of childhood atopic asthma.

Methods: In 72 pediatric patients with atopic asthma who were followed up between 2016 and 2022 with a mean follow-up period of 6.03±2.19 years, demographic characteristics, family history, clinical symptoms, pulmonary function test results, and asthma control test scores were evaluated. Totally controlled patients who had not received any asthma treatment for ≥1 year were considered to be in "clinical remission."

Results: The study group included 72 children with atopic asthma (female/male: 28/44), with a mean age of 13.36±1.98 (8-18) years. 12.5% (n=9) of the patients had uncontrolled asthma, 45.8% (n=33) were partially controlled asthma, 41.7% (n=30) were complete controlled asthma. Clinical remission was seen in 23.6% (n=17) patients with total control. Patients who were symptomatic before the age of three and had a persistent course had a lower clinical remission rate (p=0.05).

Conclusion: In our study, the clinical remission rate in atopic asthma in early adulthood was 23.6%. Our results reveal that the clinical remission rate was lower in patients who developed symptoms and had persistent wheezing before the age of three.

Keywords: Pediatric asthma, allergic asthma, asthma remission, prognostic factors, natural history

ÖZ

Amaç: Alerjik astımı olan çocuklarda prognoz ve prognozu etkileyen faktörler üzerine az sayıda çalışma yapılmıştır. Biz çalışmamızda çocukluk çağı alerjik astımının prognozunu, klinik remisyon oranını ve katkıda bulunan faktörleri değerlendirmeyi amaçladık.

Gereç ve Yöntem: 2016-2022 yılları arasında ortalama takip süresi 6,03±2,19 yıl olan alerjik astım tanılı 72 pediatrik hastada demografik özellikler, aile öyküsü, klinik semptomlar, solunum fonksiyon testi sonuçları ve astım kontrol testi skorları değerlendirildi. Bir yıldan fazla herhangi bir astım tedavisi almayan kontrollü hastalar "klinik remisyonda" kabul edildi.

Bulgular: Çalışma grubuna yaş ortalaması 13,36±1,98 olan 72 alerjik astımlı çocuk (kız/erkek: 28/44) dahil edildi. Astım kontrol durumuna göre hastaların %12,5'i (n=9) kontrolsüz, %45,8'i (n=33) kısmi kontrollü, %41,7'si (n=30) tam kontrollü idi. Tamamen kontrol altına alınan olguların %23,6'sında (n=17) klinik remisyon gözlendi. Üç yaşından önce semptomatik olan ve persistan seyirli hastalarda klinik remisyon oranı daha düşüktü (p=0,05).

Sonuç: Çalışmamızda erken çocukluk döneminde alerjik astımda klinik remisyon oranı %23,6 idi. Üç yaşından önce semptomları başlayan ve persistan seyirli olgularda klinik remisyon oranının daha düşük olduğunu saptadık.

Anahtar Kelimeler: Pediatrik astım, alerjik astım, astım remisyonu, prognostik faktörler, doğal seyir

Address for Correspondence: Ömer Akçal, İstanbul Biruni University Faculty of Medicine Hospital, Clinic of Pediatric Immunology and Allergy Diseases, İstanbul, Türkiye
Phone: +90 535 795 86 86 E-mail: omerakcal@hotmail.com ORCID ID: orcid.org/0000-0002-3046-7133

Cite as: Bahçeci Erdem S, Nacaroğlu HT, Akçal Ö. Prognosis of Childhood Atopic Asthma: A 6-year Follow-up Study. Med J Bakirkoy 2023;19:236-241

Received: 15.01.2023
Accepted: 25.04.2023

INTRODUCTION

Asthma is the most common chronic lung disease in children and a major cause of morbidity and mortality (1,2). Despite advances in treatment, it is still an incurable disease. The aim of asthma treatment is to control the disease (2,3).

While some children with asthma experience remission in their early childhood, the disease persists in some children throughout their lives (1,3). Parents ask many questions, such as, "Will my child's asthma get better?" "When will my child's asthma get better?" The answer and, however, is not so clear and may depend on many factors. It may also differ among populations based on genetic and environmental factors (3-5).

Remission in childhood asthma is most common between the ages of 14 and 21. Studies have reported variable remission rates ranging from 14 to 75%. (6,7). This variation is largely due to the lack of a standardized definition of asthma remission and the heterogeneity of the patient populations (3-5).

There is still no consensus on the definition of asthma remission. There are different definitions of what "remission" in asthma means. Remission can be either complete or clinical. "Complete remission" can be defined as occurring in patients who have received no pharmacologic treatment for ≥1 year, have no symptoms, no airway obstruction, objective evidence of the absence of asthma-related inflammation (such as reduced blood or sputum eosinophil counts, exhaled nitric oxide, and/or other relevant measures), and no bronchial hyperresponsiveness. "Clinical remission" can be defined as a patient who has not received any pharmacologic treatment for ≥1 year, has no asthma symptoms and the patient and physician agree on disease remission (2). Some patients in clinical remission with persistent bronchial hyperresponsiveness may experience recurrence of symptoms for the rest of their lives, while others do not.

The purpose of this study was to assess the prognosis, clinical remission rate, and risk factors in children with atopic asthma.

METHODS

We selected 120 patients who were diagnosed with atopic asthma according to the Global Initiative for Asthma guidelines (8), who had regular follow-up between 2016 and 2022, and who had not received allergen immunotherapy before. We tried to contact 120 patients, and 96 patients who could be reached were invited to the outpatient clinic control for re-evaluation. Seventy two of the 96 patients were re-evaluated within the specified time frame. Demographic characteristics, time of disease onset, family history, comorbidities, symptom frequency, smoking exposure (passive smoking), serum total IgE, blood eosinophil count, skin-prick test (SPT) results, body mass index (BMI), and asthma medications were recorded. The pulmonary function test and asthma control test (ACT) were repeated. Patients with an ACT score of 25 were regarded to have "total control," those with a score between 20 and 24 were regarded to have "partial control," and those with a score less than 20 were regarded to have "uncontrolled asthma" (9). Patients who were regarded to have completely controlled asthma were evaluated for remission status. Patients without asthma symptoms who had not received asthma treatment for at least a year were classified as being in "clinical remission" (2). Patients with a BMI ≥95 p were classified as obese (10).

Specific respiratory diseases (such as cystic fibrosis or tuberculosis) or other seriously interfering diseases were not included in the study. Patients who had previously received allergen immunotherapy for atopic asthma were excluded from the study (due to the effects of allergen immunotherapy on the natural course of the disease).

Skin-prick Tests

SPTs were performed by trained physicians on the volar surface of the forearm of each patient using a commercial extract (ALK Abelló, Horsholm, Denmark) with common allergens [house dust mites (Dermatophagoides pteronyssinus and D. farinae), pollens (grass, weed, and tree), molds (Alternaria, Cladosporium), animal dander (cat and dog), and food (cow's milk, egg, wheat, peanut, fish, and soy)]. The tests were always performed using a histamine-positive control and a saline-negative control. A positive result was defined as a mean wheal diameter greater than 3 mm after 15 minutes of testing the allergen extracts.

Blood Eosinophil Counts and Serum Total IgE Levels

Complete blood count was performed on the Mindray BC-6000 device with peripheral blood samples collected in EDTA tubes. Serum IgE levels were determined by the nephelometric method (Dade Behring Marburg Gmbh, Germany).

Spirometry

Forced expiratory maneuvers were measured using a spirometer (ZAN 100 USB Betterflow Spirometer, Germany). Data are presented as a percentage of the predicted values, with race, gender, body weight, and height considered. The best result after at least 3 evaluations was considered. If a patient's spirometry was not satisfactory on the first visit, the

first appropriate spirometry test result and the spirometry test results of all subjects at the last follow-up visit were evaluated.

Asthma Control Test

The control of asthma was assessed using the ACT questionnaire, which consisted of five questions regarding daytime and nighttime asthma symptoms, rescue medication use, and level of impairment in daily activities due to asthma. An ACT score of 25 points was considered total control, 20-24 points as partial control, and <20 points as uncontrolled (9).

Approval for the study was obtained from İzmir Bakırçay University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (decision no: 796, date: 30.11.2022).

Statistical Analysis

IBM SPSS version 24.0 (Armonk, New York, United States) was used for all statistical analyzes parametric methods were used for the analysis of variables with a normal distribution, whereas non-parametric methods were used for the analysis of variables that were not normally distributed. Comparisons of continuous variables were made with independent-sample t-test and Mann-Whitney U test as appropriate. Pearson's chi-square and linear-by-linear association tests were used with an exact test for the comparison of categorical data. The categorical data are expressed as a percentage of the number (n) of children evaluated. The level of significance for the analyses was $p<0.05$.

RESULTS

The study group consisted of 72 patients, 38.9% (n=28) female, 61.1% (n=44) male, mean age 13.36±1.98 years, age at diagnosis 7.54±2.51 years. In the family, atopy was present in 25% (n=18), parental asthma in 6.9% (n=5), allergic rhinitis at diagnosis in 70.8% (n=51), and multiallergen sensitization in 60% (n=36) of cases. 4.2% (n=3) of the patients were obese. Passive smoking was found in 54% (n=34) of patients at the time of diagnosis. The proportion of patients whose symptoms started before the age of 3 years and persisted was 22.5% (n=16).

According to asthma control status at follow-up, 12.5% (n=9) of the patients had uncontrolled asthma, 45.8% (n=33) had partially controlled asthma, and 41.7% (n=30) had totally controlled asthma. Clinical remission was seen in 23.6% (n=17) patients with complete control.

Patients with clinical remission were compared with those without. The clinical remission rate tended to be lower in patients who were symptomatic before the age of three years and had a persistent course (p=0.05). No significant difference was found when atopic asthma patients with and without clinical remission were compared in terms of baseline allergen sensitization, comorbid atopic disease, asthma severity, pulmonary function tests, serum total IgE levels, and eosinophil counts (Table 1).

DISCUSSION

In our study, the clinical remission rate was 23.6% (n=17) at a mean follow-up of 6 years. Patients with symptom onset and persistent wheezing before the age of three years had a lower clinical remission rate.

Remission rates in childhood asthma are different in studies. The fact that atopic and nonatopic asthma patients were chosen together and that the remission criteria used were different may explain some of the differences in remission rates between the studies.

In a 4-year follow-up, Covar et al. (3) reported that only 6% of 909 pediatric patients with atopic asthma developed clinical remission during adolescence. In the 12-year follow-up study of Wang et al. (4) in children with asthma, the clinical remission rate was reported as 26% in early adulthood.

In a 10-year follow-up study conducted by Sekerel et al. (5) in Türkiye, the clinical remission rate in 115 pediatric patients with asthma (both atopic and non-atopic) was 26%. Aydogan et al. (11) reported that in a 10-year follow-up of asthmatic children from Türkiye, the atopy status of the patients determined the persistence of asthma and that most of the nonatopic patients recovered before the age of 10 years and by the age of 18 years. They also discovered that two-thirds of asthma cases with atopy persisted. In all these studies, children with atopic and non-atopic asthma were evaluated together (3-5,11).

Only a few studies have looked at atopic factors as predictors of asthma remission. When 119 children with atopic asthma were evaluated after 30 years of follow-up at the ages of 32-42 years, the remission rate was 52% (22% complete remission, 30% clinical remission). In this study, high FEV1 values at first admission and in remission were found to be important predictors of clinical remission in children with asthma (12). In our study, the follow-up period was shorter. In terms of pulmonary function, we found no difference between the two groups. However, clinical remission was lower in patients whose respiratory symptoms began before the age of three years and persisted, despite no difference in pulmonary function tests. Lower serum IgE levels, fewer positive skin tests, and less need for medication were found

Table 1. Baseline characteristics for all participants in the study were stratified by clinical asthma remission status (n=72)

	No asthma remission (n=55)	Asthma remission (n=17)	p-value
Age (y), mean ± SD	13.29±2.09	13.58±1.62	0.593
Age at asthma diagnosis (y), mean ± SD	7.56±2.65	7.47±2.06	0.895
The duration of follow-up, year	6.03±2.19	6.11±1.86	0.891
Sex			0.825
Male	47.2% (34)	13.9% (10)	
Female	29.2% (21)	9.7% (7)	
Parental history of asthma (yes)	6.9 (5)	0.0 (0)	0.249
Familial atopic disease (yes)	16.7 (12)	8.3 (6)	0.209
Aeroallergen sensitization on skin testing			0.245
Mite	13.9 (10)	2.8 (2)	
Mold	19.4 (14)	1.4 (1)	
Pollens	6.9 (5)	4.2 (3)	
Cockroaches	1.4 (1)	0.0 (0)	
Multiallergen	34.7 (25)	25.3 (11)	
Pet at diagnosis (yes)	13.9 (10)	2.8 (2)	0.420
Hospitalization with respiratory tract infection in <3-years-old	26.8 (19)	2.8 (2)	0.057
With persistent symptoms from the first age of three years	21.1 (15)	1.4 (1)	**0.050**
Obesity at diagnosis	4.2 (3)	0.0 (0)	0.440
Allergic rhinitis at diagnosis	52.8 (38)	18.1 (13)	0.399
Additional chronic disease at diagnosis	5.6 (4)	0.0 (0)	0.332
Asthma control at diagnosis			0.668
Uncontrolled, % (n)	72.2 (52)	22.2 (16)	
Partial control, % (n)	4.2 (3)	1.4 (1)	
Passive smoking	39.7 (25)	14.3 (9)	0.591
Asthma severity at diagnosis			0.098
Mild	64.8	23.9	
Moderate	11.4	0.0	
FEV1 at diagnosis (% predicted)*	87.85±14.68	89.92±11.91	0.631
FEV1/FVC ratio at diagnosis (%)*	109.70±7.02	110.14±7.71	0.843
FEF 25-75 at diagnosis	113.95±26.16	123.07±27.73	0.435
Serum IgE level (IU/mL) at diagnosis*	277.04±297.12	223.16 ±115.10	0.147
Eosinophils (%) at diagnosis*	5.72±4.19	4.41±6.07	0.336
Eosinophil count (cells/μL) at diagnosis*	424.58±336.67	400.00±575.69	0.838

*Mean ± SD; FEV1: Forced expiratory volume in the first second, FVC: Forced vital capacity, FEF 25-75: Forced expiratory flow between 25% and 75% of vital capacity, SD: Standard deviation
Statistical significance was set at 0.05. All statistically significant values are reported in bold

to be predictive for remission in a study in which patients with moderate-to-severe atopic asthma in childhood who received allergen immunotherapy between the ages of 5 and 12 years were evaluated in young adulthood (17-30 years) (13). In our study, there were no patients who had received allergen immunotherapy before.

There are more studies on children with both atopic and non-atopic asthma. In these studies, it has been shown that better pulmonary function is associated with a better prognosis in adulthood (5,12,14). It has been reported that asthmatic adolescents with remission activity represent a distinct phenotype with milder, less atopic, and less hyperresponsive asthma during school years (3). Wang et al. (4) found in a 12-year follow-up study that the most important determinant of asthma remission was the severity of airway obstruction. According to Sekerel et al. (5), decreased airflow, female gender, and eosinophilia appears to predict the "adverse outcome" of childhood asthma. According to some studies, asthma remission rates differ significantly among populations. In these studies, remission was associated with less-allergic sensitivity, milder asthma severity at diagnosis, and male gender (7,15,16). In our study, no difference was found in terms of allergen sensitization, baseline asthma severity, or gender. Stern et al. (16) reported in a birth cohort study that persistent wheezing early in life was one of the factors associated with asthma at the age of 22 years. In our study, we came to a similar conclusion.

According to Aydogan et al. (11), asthma persists in the presence of bronchial hyperresponsiveness and rhinitis. In our study, 70.8% (n=51) of the patients were accompanied by allergic rhinitis, and there was no difference between the group with and without clinical remission in terms of the association of allergic rhinitis.

Our study had several limitations, including the fact that it was retrospective, the number of cases was small (Participants were included in the study provided that they had been receiving regular follow-up since 2016. This is a factor limiting the number of cases) and the patients could not be evaluated for complete remission. Our study included only patients with mild to moderate persistent childhood atopic asthma. Another limitation of our study is that it does not include mild intermittent or severe atopic asthma cases.

CONCLUSION

Childhood asthma usually has a high remission rate. However, there are few studies evaluating remission, especially in atopic asthma. Our study, which was conducted in children with atopic asthma who were symptomatic before the age of three years and had a persistent course, found that the rate of clinical remission was lower. More research is required to determine which factors play a role in predicting remission in children with atopic asthma. The data will help doctors and parents make decisions about the prognosis of childhood atopic asthma.

ETHICS

Ethics Committee Approval: Approval for the study was obtained from İzmir Bakırçay University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (decision no: 796, date: 30.11.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.B.E., H.T.N., Ö.A., Concept: S.B.E., Ö.A., Design: S.B.E., H.T.N., Ö.A., Data Collection or Processing: S.B.E., H.T.N., Analysis or Interpretation: S.B.E., Ö.A., Literature Search: S.B.E., H.T.N., Ö.A., Writing: S.B.E., H.T.N., Ö.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Belsky DW, Sears MR. The potential to predict the course of childhood asthma. Expert Rev Respir Med 2014;8:137-41.
2. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert consensus framework for asthma remission as a treatment goal. J Allergy Clin Immunol 2020;145:757-65.
3. Covar RA, Strunk R, Zeiger RS, Wilson LA, Liu AH, Weiss S, et al. Predictors of remitting, periodic, and persistent childhood asthma. J Allergy Clin Immunol 2010;125:359-66.
4. Wang AL, Datta S, Weiss ST, Tantisira KG. Remission of persistent childhood asthma: Early predictors of adult outcomes. J Allergy Clin Immunol 2019;143:1752-9.
5. Sekerel BE, Civelek E, Karabulut E, Yildirim S, Tuncer A, Adalioglu G. Are risk factors of childhood asthma predicting disease persistence in early adulthood different in the developing world? Allergy 2006;61:869-77.
6. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med 2003;349:1414-22.
7. Tai A, Tran H, Roberts M, Clarke N, Gibson AM, Vidmar S, et al. Outcomes of childhood asthma to the age of 50 years. J Allergy Clin Immunol 2014;133:1572-8.
8. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2016. Available from: www.ginasthma.org
9. Uysal MA, Mungan D, Yorgancioglu A, Yildiz F, Akgun M, Gemicioglu B, et al. The validation of the Turkish version of Asthma Control Test. Qual Life Res 2013;22:1773-9. Erratum in: Qual Life Res 2013;22:1781-2.
10. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2017;102:709-57.
11. Aydogan M, Ozen A, Akkoc T, Eifan AO, Aktas E, Deniz G, et al. Risk factors for persistence of asthma in children: 10-year follow-up. J Asthma 2013;50:938-44.

12. Vonk JM, Postma DS, Boezen HM, Grol MH, Schouten JP, Koëter GH, et al. Childhood factors associated with asthma remission after 30 year follow up. Thorax 2004;59:925-9.
13. Limb SL, Brown KC, Wood RA, Wise RA, Eggleston PA, Tonascia J, et al. Adult asthma severity in individuals with a history of childhood asthma. J Allergy Clin Immunol 2005;115:61-6.
14. Godden DJ, Ross S, Abdalla M, McMurray D, Douglas A, Oldman D, et al. Outcome of wheeze in childhood. Symptoms and pulmonary function 25 years later. Am J Respir Crit Care Med 1994;149:106-12.
15. Andersson M, Hedman L, Bjerg A, Forsberg B, Lundbäck B, Rönmark E. Remission and persistence of asthma followed from 7 to 19 years of age. Pediatrics 2013;132:e435-42.
16. Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. Lancet 2008;372:1058-64.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:242-247
DOI: 10.4274/BMJ.galenos.2023.2023.3-3

Research

Assessment of Carotid-vertebral Artery and Renal Artery Doppler Ultrasound in the Behçet's Disease with Cutaneous Lesions

Kutanöz Lezyonları Bulunan Behçet Olgularında Karotis-vertebral Arter ve Renal Arter Doppler Ultrasonografi Bulgularının Değerlendirilmesi

İsmail Yurtsever

Bezmialem Vakıf University Faculty of Medicine, Department of Radiology, İstanbul, Türkiye

ABSTRACT

Objective: Behçet's disease (BD) is a chronic multisystem inflammatory disease of unknown etiology defined as recurrent aphthous oral and genital ulcers, skin lesions, and uveitis. BD is a type of systemic vasculitis that can affect arteries regardless of origin and size-the co-occurrence of chronic systemic vasculitis and acute systemic inflammation results in an endothelial abnormality of the vessels. The morphological thickness of the arterial wall is a crucial feature of atherosclerosis. Carotid intima-media thickness (IMT) is an endothelial cell dysfunction parameter associated with atherosclerosis. This study aimed to evaluate the hemodynamic properties of carotid-vertebral and renal arteries of BD with cutaneous lesions to prove the effects of subclinical morphology of atherosclerosis.

Methods: The study consisted of 23 BD patients with oral and genital aphthae or cutaneous lesions. Color Doppler and B-mode ultrasonography examinations of the carotid-vertebral and renal arteries were performed in all patients. The assessment of the vascular structures included IMT, plaque thickness, resistive index, pulsatility index, peak systolic velocity, end-diastolic velocity, and the volumes of both kidneys were measured in the study. In addition, the flow rates of both vertebral arteries were calculated.

Results: The most intriguing findings of our study were the detection of non-stenotic plaque in 3 patients, mild intimal thickening in most patients, and vertebra basilar insufficiency in 12 patients. In addition, hemodynamic alterations of the patient's carotid arteries were compatible with the reported findings in the literature. Age, gender, disease duration, ophthalmic and neurological involvement, and IMT correlation were evaluated with the chi-square test, and no statistically significant correlation was found in this study. However, in the Mann-Whitney U test, a significant positive correlation was detected between kidney volume and IMT ($p<0.035$).

Conclusion: We found no significant differences in vascular changes secondary to early atherosclerosis compared with the average population and literature in Behçet patients with cutaneous lesions. The increase in kidney size may be one of the early signs of atherosclerosis in Behçet's cases.

Keywords: Behçet's disease, carotid-vertebral Doppler, intima-media thickness, renal artery Doppler

ÖZ

Amaç: Behçet hastalığı (BH), etiyolojisi bilinmeyen, esas olarak tekrarlayan aftöz oral ve genital ülserler, deri lezyonları ve üveit ile karakterize, kronik, tekrarlayan, multisistemik enflamatuvar bir hastalıktır. BH, insan vücudundaki orjini ve büyüklüğü ne olursa olsun her arteri etkileyebilen bir sistemik vaskülittir. Akut sistemik enflamasyon ve kronik sistemik vaskülitin birlikte ortaya çıkması damarın endotel disfonksiyonuna neden olabilir. Arteriyel duvarın morfolojik kalınlığı aterosklerozun önemli bir özelliğidir. Karotis intima-media kalınlığı (İMK), ateroskleroz ile ilişkili bir endotelyal disfonksiyon parametresidir. Bu çalışmada, kutanöz lezyonları olan Behçet hastalarının karotis-vertebral ve renal arterlerinin hemodinamik özelliklerinin karşılaştırılarak aterosklerozun subklinik morfolojisinin etkilerinin kanıtlanması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya oral ve genital aft veya kutanöz lezyonları olan 23 Behçet hastası alındı. Hastalara karotis-vertebral ve renal arterlerin renkli Doppler ve B-mod ultrasonografi incelemeleri yapıldı. Vasküler yapıların incelenmesinde İMK, plak kalınlığı, pik sistolik hız, diyastol sonu hız, rezistif indeks, pulsatilite indeksi değerlendirilerek her iki böbreğin hacimleri ölçüldü. Ek olarak, her iki vertebral arterin akım hızları hesaplandı.

Address for Correspondence: İsmail Yurtsever, Bezmialem Vakıf University Faculty of Medicine, Department of Radiology, İstanbul, Türkiye
Phone: +90 212 453 17 00 E-mail: dryurtsever@hotmail.com ORCID ID: orcid.org/0000-0001-7482-668X

Cite as: Yurtsever İ. Assessment of Carotid-vertebral Artery and Renal Artery Doppler Ultrasound in the Behçet's Disease with Cutaneous Lesions. Med J Bakirkoy 2023;19:242-247

Received: 23.03.2023
Accepted: 22.05.2023

Bulgular: Çalışmamızın en ilgi çekici bulguları 3 hastada stenotik olmayan plak, çoğu hastada hafif intimal kalınlaşma ve 12 hastada vertebrobaziler yetmezlik saptanmasıdır. Hastaların karotis arterlerindeki hemodinamik değişiklikler literatürde bildirilen bulgularla uyumluydu. Ki-kare testi ile yaş, cinsiyet, hastalık süresi, oftalmik ve nörolojik tutulum ve İMK korelasyonu değerlendirildi. Çalışmamızda istatistiksel olarak anlamlı korelasyon saptanmadı. Ancak Mann-Whitney U testinde böbrek hacmi ile İMK arasında anlamlı pozitif korelasyon saptandı (p<0,035).

Sonuç: Behçet'in kutanöz lezyonlu hastalarında erken ateroskleroza sekonder vasküler değişikliklerde normal popülasyona ve literatüre göre anlamlı bir fark bulunamadı. Böbrek büyüklüğündeki artış, Behçet olgularında damar sertliğinin erken belirtilerinden biri olabilir.

Anahtar Kelimeler: Behçet hastalığı, karotid-vertebral arter Doppler, intima-media kalınlığı, renal arter Doppler

INTRODUCTION

Turkish dermatologist Hulusi Behçet (1889-1948), who identified and published a triad of symptoms in 1937, is credited with giving the disease its name, Behçet's disease (BD), a multisystem inflammatory condition with an unknown cause. BD is more common in populations carrying the *HLA-B5* gene (1). Aphthous mouth ulcers, genital ulcers, and skin lesions are the main symptoms of BD, a multisystemic inflammatory condition that is chronic, recurring, and has an unknown etiology (2). A wide range of systemic organ involvement occurs in BD, such as in the vascular, ophthalmic, central nervous system, musculoskeletal, and gastrointestinal systems. Obliterative vasculitis is the central lesion in BD, which may be brought on by aberrant immune complexes that circulate in the blood (2,3).

Deep vein thrombosis (DVT), myocardial infarction, arterial aneurysm, and formation of an arterial thrombus have all been documented in about 20-35% of instances in patients with BD, primarily in male individuals (2). These complications usually occur in male patients (2). A defining aspect of BD is histological evidence of vasculitis with endothelial cell activation or damage (4). Carotid intima-media thickness (IMT) is a parameter associated with atherosclerosis and endothelial vessel dysfunction (4).

This study assessed the vascular involvement of BD patients with cutaneous lesions. We assumed that BD patients might have a greater risk in the cardiovascular system; thus, the morphological evidence of subclinical atherosclerosis was investigated and evaluated with high-resolution B-mode ultrasonography (U/S) and Doppler U/S of the carotid, vertebral, and renal arteries.

METHODS

Study Design and Patients

Twenty-three cases with oral and genital aphthale or cutaneous lesions diagnosed with BD and followed up at the department of dermatology in a university hospital were included in this study. All of our cases were under treatment and had mild symptoms. Of the patients, 12 were women and 11 were men, with a mean age of 39 years for women and 46 years for men. Exclusion criteria for all participants were defined as wholly healed cutaneous lesions and/or patients with BD with no clinical manifestation of cutaneous lesions.

Patient Evaluation

The same radiologist performed all Doppler U/S exams without knowing the clinical condition of the patients and used the same scanner: a Toshiba (Applio 500; Toshiba, Tokyo, Japan) equipped with a 14-mm-wide, 7.5-MHz linear array transducer. Duplex and color Doppler U/S was examined on the patients' and the control groups' carotid and renal arteries. Doppler U/S examinations of all patients were lying down in the supine position, and the carotid and renal arteries were evaluated; for the common carotid artery (CCA) and internal carotid artery (ICA), flow measurements were taken 2 cm proximal and 2 cm distal to the bulb, respectively, measuring the peak systolic (PSV), end-diastolic (EDV), and time-averaged edged mean (Vmean) velocity for each artery. The system computed the resistance (RI) and pulsatility index (PI) from these measurements. During the Doppler U/S evaluation, none of the patients took any medicine (including oral and topical anti-inflammatory drugs, etc.) that would have affected the findings. The Bezmialem Vakıf University Ethics Committee approved the study with reference number 2022/338 (date: 24.01.2023). Informed consent of all study participants was obtained before the U/S evaluation.

Carotid Artery Evaluation by B-mode Ultrasound Measurement Technique

The intima-media complex is represented by the leading margins of the lumen-intima and media-adventitia interfaces (the "double-line pattern") of the arterial wall in longitudinal pictures of the carotid arteries used for IMT measurements (5,6). Normal common carotid IMT was typically 0.4 to 0.5 mm at age 10, but by the fifth decade of life, it had increased to 0.7 to 0.8 mm or more (7). The plaque was characterized as either an apparent protrusion of more than 1.5 mm into the artery lumen or as clear echogenicity with a posterior echogenic shadow (4,8).

Statistical Analysis

Descriptive statistics include frequency, percentage, and median (minimum-maximum). Analyses were made with Fisher's exact chi-square test and Mann-Whitney U test in the SPSS 28 V program. The significance level was taken as α=0.05.

RESULTS

The median age was 40.0 (25.0-66.0) years for 23 people with BD included in our study, and the median disease duration was 8.0 (2.0-23.0) years for these patients. The study control group had the exact number and similar proportion of healthy individuals. Previous clinical findings of BD are shown in Tables 1 and 2. The demographic and clinical characteristics of the participants are shown in Table 1. The clinical features of the patients were compared according to whether they showed any sign of neurological symptoms, and their findings are given in Table 2. No statistically significant difference was observed among neuro-Behçet's diseased patients who manifested neurological signs or not and Behçet's patients with increased intimal thickness and ophthalmic findings (p>0.05). However, kidney size was significantly increased in patients with an increased intimal thickness of the carotid arteries (p=0.035).

In our cases, three smooth-surfaced atherosclerotic soft plaques, which were hemodynamically insignificant, were observed in the CCA bulb. The largest of them was measured at 7.7x1.7 mm. None of the BD patients in this study had a hemodynamically significant atherosclerotic plaque. The IMT of the correct CCA was counted as 0.8 mm in 17 of our cases, 1.0 mm in 2 cases, 1.1 mm in 1 case, 1.2 mm in 2 points, and 1.3 mm in 1 patient. IMT was measured 0.8 mm in 19 of the left CCA, 0.9 mm in 1 case, 1.0 mm in 1 point, and 1.2 mm in 2 cases (Figure 1). There was no disease activity during and in the month before the study. In BD patients, Carotid IMT values were slightly higher than in the control group [0.80 (0.80-1.30) vs. 0.7±0.1 mm]. However, cardiac and significant vessel involvement were not detected. In 12 cases, the total vertebral artery flow rate was less than 200 mL/min, consistent with vertebrobasilar insufficiency. In our study, IMT values did not correlate with the duration of the disease, neuro-BD, or ophthalmic and vascular involvement. In the spectral examination of both kidneys of our BD patients, RI (RI 0.60±0.05) and PI (1.05±0.18) values were within normal limits.

DISCUSSION

In the literature, BD is accepted as an unclassified vasculitis affecting arteries and veins of all sizes (9). Clinical manifestations of BD include mucocutaneous, ocular, articular, vascular, and neurological involvement, along with all other organ systems (10). Mucocutaneous involvements, which include oral ulcers, genital ulcers, and cutaneous lesions, are thought to be the "fingerprint" of the disease because they are the most common and frequently the first symptoms to manifest (10,11).

Table 1. Demographic and clinical informations of patients with Behçet's disease

	Median (minimum-maximum) (n=23) n (%)
Age, years (mean)	40.0 (25.0-66.0)
Disease duration (years)	8.0 (2.0-23.0)
Gender	
Female	12 (52.2)
Male	11 (47.8)
Skin and mucosal involvement	
Aphthous oral and genital ulcers	21 (91.3)
Presence of nodules	2 (8.7)
Neuro-Behçet's	
Negative	4 (17.4)
Neurologic symptoms	19 (82.6)
Vascular involvement	
Negative	16 (69.6)
Trombophlebitis	5 (21.7)
Retinopathy	2 (8.7)
Ophtalmic involvement	
Negative	14 (60.9)
Positive	9 (39.1)
Iridocyclitis	
Negative	19 (82.6)
Positive	4 (17.4)
Uveitis	
Negative	17 (73.9)
Positive	6 (26.1)
R_carotis intimal thickness	
Mild	14 (60.9)
Increase	9 (39.1)
L_carotis intimal thickness	
Mild	18 (78.3)
Increase	5 (21.7)

Table 2. Clinical comparisons by neuro-Behçet's condition

	Neuro-Behçet's		
	Negative (n=4)	**Neurologic symptoms (n=19)**	**p-value**
Disease duration (years)	9.0 (5.0-23.0)	8.0 (2.0-19.0)	0.745
R_carotis intimal thickness			
Mild	2 (50)	12 (63.2)	1.000
Increase	2 (50)	7 (36.8)	
L_carotis intimal thickness			
Mild	3 (75.0)	15 (78.9)	1.000
Increase	1 (25.0)	4 (21.1)	
Ophtalmic involvement			
Negative	2 (50)	12 (63.2)	1.000
Positive	2 (50)	7 (36.8)	
Uveitis			
Negative	4 (100.0)	13 (68.4)	0.539
Positive	0 (0.0)	6 (31.6)	
Ophtalmic involvement			
Negative	3 (75.0)	16 (84.2)	1.000
Iridocyclitis	1 (25.0)	3 (15.8)	
Renal volume	**Bilateral carotis intimal thickness increase (n=9)**	**Bilateral carotis intimal thickness normal (n=14)**	0.035
	287.0 (167.0-387.0)	243.5 (188.0-377.0)	

Data are shown as median (minimum-maximum) and frequency and percentage

BD eye involvement presents as non-granulomatous, bilateral, and recurrent inflammation of the anterior uvea. There are three primary forms of posterior segment changes: retinitis, widespread vascular leakage, and retinal vasculitis, predominantly affecting veins (2,3). In addition, bilateral eye involvement and recurrent episodes of uveitis may cause progressive vision loss (3,10). Neurosyndrome Behçet is the term used to describe the predominant neurological involvement in BD (neuro-Behçet's syndrome) (12).

Recurrent inflammation defines BD, which is an occlusive vasculitis (3,13). Venous involvement exceeds arterial participation by 75% to 25% (2-4). Therefore, the most frequent symptom is DVT in the lower extremity (4).

Chronic inflammation is an infrequent risk factor for the development of atherosclerosis (4,13). Nowadays, atherosclerosis is mainly perceived as a persistent, low-grade inflammatory condition. Endothelial damage is a crucial stage in atherogenesis and a defining trait of BD (4,6,14). Due to this fact, in this study, carotid arteries in BD patients were assessed. Blood vessels of all diameters are affected by BD, a systemic disease (14).

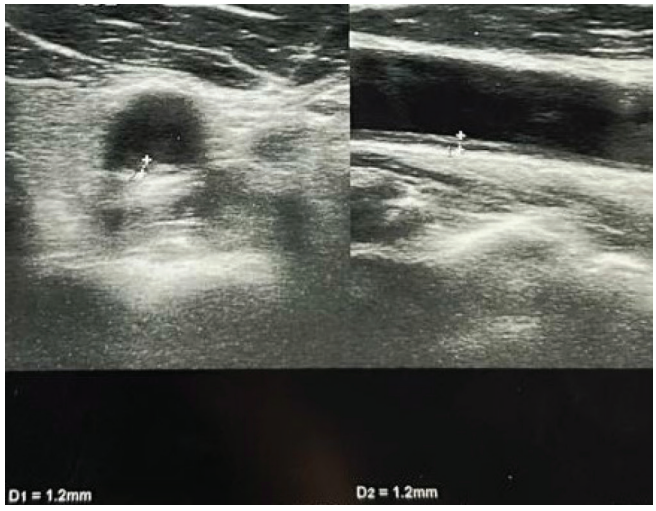

Figure 1. Intimal thickness measurement from the carotid artery

Doppler ultrasound has emerged as a popular, simple, manageable, affordable, quick, precise, and noninvasive tool for measuring vascular hemodynamics. We reasoned that since vascular illness affects all vessel diameters and is a prevalent clinical characteristic of BD, the carotid arteries may be affected (14).

Subclinical atherosclerosis can be detected by measuring carotid IMT using high-resolution B-mode U/S. Endothelial injury is a critical event in atherogenesis. A crucial characteristic of atherosclerosis is the morphological thickness of the arterial wall (15). Unfortunately, we could not show a relationship between carotid IMT and disease severity scores in patient groups. Similar to the current study, only 3% to 4% of the carotid arteries in Behçet patients had atherosclerotic plaques (14). Our study found a similar proportion of atherosclerotic plaques in CCA. Akçar et al. (14) reported no atherosclerotic plaques in the carotid arteries of 41 BD patients.

Various studies have reported significantly higher IMT in BD patients than in controls (4,8,15,16). However, in another study, the authors reported no difference in IMT measurements between her BD patients and controls (2). In our study, BD carotid artery IMT scores were slightly higher than those of healthy subjects, but not significantly. Similarly, Messedi et al. (2) we found no significant association between IMT and clinical and therapeutic disease features in our BD patients.

In addition, our study could not find a statistically significant relationship between IMT and clinical involvement areas.

Among the various parameters, only age was positively correlated with carotid IMT in both BD patients and controls (15). Similarly, we could not show a correlation between the clinical severity of the disease and carotid IMT in our patient group.

In BD patients, higher IMT was substantially linked with signs of endothelial dysfunction, according to a recent study (4). However, according to the research, there was disagreement on the connection between IMT measures in individuals with BD and cardiovascular risk factors (2).

Typical or nontraditional risk factors for cardiovascular disease do not predict increased IMT during this systemic vasculitis. Furthermore, the immunosuppressive medication, the length of the illness, or clinical signs were not linked to increased artery wall thickness. These findings imply that BD might result in elevated IMT (2).

Moreover, vascular involvement, posterior uveitis, or retinal vasculitis have all been linked to IMT by other authors (2). Although plaque incidence was often higher in BD than in healthy controls, this difference was not statistically significant. This divergence in IMT-related parameters in BD patients seen in the literature may be caused by variations in vascular risk factors among various ethnic groups (2). These vascular risk factor variations between ethnic groups are most likely hereditary. These findings suggest that atherogenesis may be influenced by prolonged systemic inflammation (2).

Renal involvement associated with BD varies significantly in different studies (17,18). Akpolat et al. (18) In their study of BD patients with renal involvement, the most prominent findings were edema-nephrotic syndrome, macroscopic hematuria, and proteinuria. More rarely, renal vasculitis, glomerulonephritis, amyloidosis, and chronic renal failure have been reported (18). Our study showed no statistically significant change in RI, PI, PSV, and EDV values on renal artery Doppler examination. Only B-mode U/S examination revealed a positive correlation between kidney volume and carotid IMT. We did not observe hematuria, proteinuria, or renal failure in the cases in our study. Not many studies in the literature show changes in renal artery Doppler parameters.

In this study, the carotid IMT of BD patients was the only positively correlated with age. However, there was no correlation between disease duration and neurological and vascular involvement. Also, in our study, it was very intriguing to find a positive correlation between carotid IMT and increase in kidney volume size in BD.

This study had some limitations. First of all, this study had a relatively small sample size. Second, it was impossible to avoid patient selection bias because all data were obtained from a single center. The exclusion of patients with further types of carotid and renal pathology, diabetes mellitus, systemic hypertension, or background with any systemic disease was another study constraint. Finally, whether illness severity raises the likelihood of subclinical atherosclerosis in BD patients cleared from further research on people with more severe diseases.

CONCLUSION

The carotid IMT was higher in the BD patients than in the healthy control group in those without substantial cardiovascular involvement. Our findings show the morphological evidence of subclinical atherosclerosis in BD. However, atherosclerosis started before clinical symptoms and may present for years. Hence, future clinical atherosclerosis events in BD may not always be predicted by increased carotid IMT and increased plaque prevalence in the carotid arteries.

ETHICS

Ethics Committee Approval: The Bezmialem Vakıf University Ethics Committee approved the study with reference number 2022/338 (date: 24.01.2023).

Informed Consent: Informed consent of all study participants was obtained before the U/S evaluation.

Financial Disclosure: The author declare that this study received no financial support.

REFERENCES

1. Duranoğlu Y, Apaydin C, Karaali K, Yücel I, Apaydin A. Color Doppler imaging of the orbital vessels in Behçet's disease. Ophthalmologica 2001;215:8-15.
2. Messedi M, Frigui M, Ben Mahfoudh K, Feki H, Ben Mahfoudh ST, Mnif J, et al. Intima-media thickness of carotid artery in patients with Behçet's disease. Arch Med Res 2011;42:398-404.
3. Caça I, Nazaroğlu H, Unlü K, Cakmak SS, Ari S, Sakalar YB. Color doppler imaging of ocular hemodynamic changes in Behçet's disease. Jpn J Ophthalmol 2004;48:101-5.
4. Hong SN, Park JC, Yoon NS, Lee SR, Kim KH, Hong YJ, et al. Carotid artery intima-media thickness in Behcet's disease patients without significant cardiovascular involvement. Korean J Intern Med 2008;23:87-93.
5. de Groot E, van Leuven SI, Duivenvoorden R, Meuwese MC, Akdim F, Bots ML, et al. Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. Nat Clin Pract Cardiovasc Med 2008;5:280-8.
6. Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC Cardiovasc Imaging 2014;7:1025-38.
7. Simova I. Intima-media thickness: Appropriate evaluation and proper measurement describes. E-Journal of the ESC Council for Cardiology Practice 2015;13:1.

8. Keser G, Aksu K, Tamsel S, Ozmen M, Kitapcioglu G, Kabaroglu C, et al. Increased thickness of the carotid artery intima-media assessed by ultrasonography in Behçet's disease. Clin Exp Rheumatol 2005;23(4 Suppl 38):S71-6.
9. Caliskan M, Gullu H, Yilmaz S, Ciftci O, Erdogan D, Dursun R, et al. Cardiovascular prognostic value of vascular involvement in Behcet's disease. Int J Cardiol 2008;125:428-30.
10. Alpsoy E, Leccese P, Emmi G, Ohno S. Treatment of Behçet's Disease: An Algorithmic Multidisciplinary Approach. Front Med (Lausanne) 2021;8:624795.
11. Uva L, Miguel D, Pinheiro C, Filipe P, Freitas JP. Mucocutaneous manifestations of Behçet's disease. Acta Reumatol Port 2013;38:77-90.
12. Uygunoglu U, Saip S, Siva A. Behçet's Disease and Neuro-Behçet's Syndrome. EMJ Neurol 2018;6:77-85.
13. Yücel Ç, Omma A, Sertoğlu E, Sezer S, Turhan T, Özgürtaş T. Evaluation of atherogenic laboratory markers in Behçet's disease patients with vascular involvement. Arch Med Sci 2019;16:531-7.
14. Akçar N, Göktekin F, Ozer A, Korkmaz C. Doppler sonography of ocular and carotid arteries in Behçet patients. J Clin Ultrasound 2010;38:486-92.
15. Oztürk MA, Oktar SO, Unverdi S, Ureten K, Göker B, Haznedaroglu S, et al. Morphologic evidence of subclinical atherosclerosis obtained by carotid ultrasonography in patients with Behcet's disease. Rheumatol Int 2006;26:867-72.
16. Alan S, Ulgen MS, Akdeniz S, Alan B, Toprak N. Intima-media thickness and arterial distensibility in Behçet's disease. Angiology 2004;55:413-9.
17. Ozel D, Ozel BD, Ozkan F, Kutlu R. Evalution of Renal Involvement in Patients with Behçet Disease: Need to be Aware About Potential Hypertension in Long Term Follow Up? Pol J Radiol 2016;81:5-9.
18. Akpolat T, Dilek M, Aksu K, Keser G, Toprak O, Cirit M, et al. Renal Behçet's disease: an update. Semin Arthritis Rheum 2008;38:241-8.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:248-255
DOI: 10.4274/BMJ.galenos.2023.2023.3-9

Research

Investigation of the Effects of Juglone-Selenium Treatments on Epithelial-Mesenchimal Transition and Migration in BxPC-3 and PANC-1 Human Pancreatic Cancer Cells

Juglon-selenyum Uygulamalarının BxPC-3 ve PANC-1 İnsan Pankreatik Kanser Hücrelerinde Epitelyal-mezenkimal Geçiş ve Migrasyon Üzerindeki Etkilerinin Araştırılması

Dudu Erkoç Kaya, Fatma Göktürk, Fatma Batırbek, Hilal Arıkoğlu

Selçuk University Faculty of Medicine, Department of Medical Biology, Konya, Türkiye

ABSTRACT

Objective: Chemotherapy is still the most common and primary treatment option for treating pancreatic cancers because metastasis has already occurred at the time of diagnosis, difficulties of the operation due to its location, and lack of targeted treatment approaches. Moreover, the high chemoteuropatic resistance seen in pancreatic cancer makes research on alternative drug treatments mandatory. Juglone, a natural naphthaquinone found in members of the Juglandaceae family, has various pharmacological effects such as antiviral and antibacterial. It has also been shown to be an effective cytotoxic agent through the production of reactive oxygen species in studies conducted with cancer cell lines. Remarkably, selenium, an important trace element of the cell, was shown to inhibit metastasis, strengthen cell-cell attachments, and reduce angiogenesis. Based on these data, we investigated the effects of juglone-selenium (J/S) combination on epithelial-mesenchymal transition (EMT) and migration in PANC-1 and BxPC-3 cells.

Methods: The effects of juglone application in the presence of 2,5 μM NaSe at 5, 10, 15 and 20 μM concentrations on the expression of *FOXL1*, *VIM*, and *MMP-7* genes were determined by qPCR. In addition, the effects of J/S on the migration features of cancer cells were monitored by wound healing tests.

Results: According to qPCR results, J/S application showed different effects on *FOXL1*, *VIM*, and *MMP-7* gene expressions, which are critical for EMT, in both cell lines. According to the wound healing assay results, the migration of cancer cells was suppressed in both cell lines compared with the control group.

Conclusion: Consequently, our studies have supported that juglone can be an effective therapeutic agent on pancreatic cancer, and our findings also suggest that selenium can strengthen these anticancer effects of juglone.

Keywords: Juglone, selenium, pancreatic cancer, epithelial-mesenchymal transition (EMT), wound-healing assay

ÖZ

Amaç: Pankreas kanserinde; tanı sırasında metastazın gerçekleşmiş olması, konumu nedeniyle cerrahi operasyonun zorluğu ve hedefe yönelik tedavi yaklaşımlarının bulunmaması sebebiyle, kemoterapi tedavi için halen en yaygın ve birincil tedavi seçeneğidir. Pankreas kanserinde görülen yüksek kemoterapötik direnç, alternatif ilaç tedavileri geliştirmek için yapılacak araştırmaları zorunlu kılmaktadır. Juglandaceae familyasının üyelerinde bulunan doğal bir naftakinon olan juglon, antiviral, antibakteriyel vb. çeşitli farmakolojik etkilere sahiptir. Kanser hücre hatları ile yapılan çalışmalarda reaktif oksijen türlerinin üretimi yoluyla etkili bir sitotoksik ajan olduğu da gösterilmiştir. Selenyum, hücrenin önemli bir eser elementidir ve dikkat çekici bir şekilde, metastazı inhibe etme, hücre-hücre bağlarını güçlendirme ve anjiyogenezde azalmaya yol açacak etkilerinin olabileceği gösterilmiştir. Bu verilerden yola çıkarak çalışmamızda, juglon-selenyum (J/S) kombinasyonunun PANC-1 ve BxPC-3 hücrelerinde epitelyal-mezenkimal geçiş (EMT) ve göç üzerindeki etkileri araştırıldı.

Address for Correspondence: Dudu Erkoç Kaya, Selçuk University Faculty of Medicine, Department of Medical Biology, Konya, Türkiye
Phone: +90 332 224 38 41 E-mail: dudu_erkoc@hotmail.com ORCID ID: orcid.org/0000-0003-0114-6602

Cite as: Erkoç Kaya D, Göktürk F, Batırbek F, Arıkoğlu H. Investigation of the Effects of Juglone-Selenium Treatments on Epithelial-Mesenchimal Transition and Migration in Bxpc-3 and Panc-1 Human Pancreatic Cancer Cells. Med J Bakirkoy 2023;19:248-255

Received: 24.03.2023
Accepted: 22.05.2023

Gereç ve Yöntem: 2,5 µM NaSe varlığında 5, 10, 15 ve 20 µM konsantrasyonlarda juglon uygulamasının *FOXL1, VIM, MMP-7* genlerinin ekspresyonu üzerindeki etkisi qPCR yöntemi ile belirlendi. Ayrıca J/S'nin kanser hücrelerinin migrasyon özellikleri üzerindeki etkileri yara iyileştirme testleri ile değerlendirildi.

Bulgular: qPCR sonuçlarımıza göre, J/S uygulaması EMT için kritik olan *FOXL1, VIM* ve *MMP-7* gen ifadeleri üzerinde her iki hücre hattında farklı düzeyde etki gösterdi. Yara iyileşme testi sonuçlarına göre ise, kontrol grubuna kıyasla her iki hücre hattında da migrasyonun baskılandığı görüldü.

Sonuç: Çalışmalarımız juglonun pankreas kanseri üzerinde etkili bir terapötik ajan olabileceğini desteklemektedir ve ayrıca bulgularımız selenyumun juglonun bu etkilerini güçlendirebileceğini düşündürmektedir.

Anahtar Kelimeler: Juglon, selenyum, pankreas kanseri, epitelyal-mezenkimal geçiş (EMT), yara iyileştirme testi

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of pancreatic cancer (PC), which is known to have poor prognosis and high mortality rates that cannot be detected at an early stage owing to lack of obvious symptoms during its development and metastasis (1,2). The 5-year survival rate is only 9%, and its incidence has been steadily increasing worldwide recently. It is considered as the fourth leading cause of cancer-related deaths in both men and women of all ages in the United States and is expected to be the second leading cause of cancer-related deaths in the western world by 2030 (2,3).

When PC is diagnosed, tumor metastases to regional lymph nodes are already seen in more than 80% of patients (4,5). Metastasis is a multistage and complex process, and can develop because of the interaction of steps such as adhesion, invasion, and angiogenesis (6). Gaining invasive properties of the tumor is the first step for metastasis. This process is called epithelial-mesenchymal transition (EMT) in epithelial-derived cancer cells. EMT is a biological process in which polarized epithelial cells undergo various molecular modifications, resulting in increased migration and mesenchymal characteristics such as invasiveness and resistance to apoptosis. The tumor microenvironment triggers EMT with many factors, including cytokines, growth factors, and chemokines (7,8).

The tumor microenvironment (TME), consisting of cancer cells, stromal cells, and extracellular components, plays a critical role in PC progression. Cancer cells and stromal cells such as pancreatic stellate cells and regulatory T-cells etc. can secrete extracellular components, including extracellular matrix (ECM), matrix metalloproteinase (MMP), growth factors, and transforming growth factor-β to maintain the microenvironment (7,8). ECM enables interactions between structural proteins and other matrix components necessary for the maintenance of tissue integrity (8). Two hallmarks of the PC microenvironment are intense desmoplasia and diffuse immunosuppression. These two features facilitate PC cell proliferation to evade the immune system through direct inhibition of antitumor immunity or induction of immunosuppressive cell proliferation (9). Desmoplasia creates a hypoxic microenvironment by increasing the functions of antiangiogenic factors. Hypoxia caused by an inadequate vascular system is essential for tumor aggressiveness, including metabolic reprograming apoptosis inhibition, continuous proliferation, resistance to treatment, invasion, and metastasis (7,10).

Unfortunately, only about 20% of patients are suitable for surgery, and in most patients, the tumor is very advanced locally or has spread to distant sites, hampering the precluding surgical intervention (11,12). Although radiation and immunotherapy are also potential options, chemotherapy is currently considered the main method to treat patients with PDAC who are not suitable for resection (13).

Gemcitabine, an antimetabolite, is an anticancer drug used to treat PC. Despite extensive research to develop new treatment methods for PC, gemcitabine still remains to be used as a chemotherapeutic agent because resistance to most conventional chemotherapeutic agents such as paclitaxel, doxorubicin, and cisplatin has been observed in clinical management (14,15). Although the combination of FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan) is the commonly used first-line systemic therapy, there is a need to find better combination therapies that can offer better efficacy and less toxicity at lower doses due to the limitations of their toxic effects (15). De novo chemoresistance to chemotherapeutic agents and/or radiotherapy is observed in PC treatment. However, current treatment options are not sufficient for curative outcomes. Therefore, there is a strong need to develop new therapeutic strategies for the treatment of PC (16-18).

Naturally occurring quinones such as thymoquinone, plumbagin, and juglone have been suggested as promising anticancer agents on different cancer cells (19). Juglone has been showed as having effective cytotoxicity through the production of reactive oxygen species (ROS) in studies with cancer cell lines. It is known that the increase in ROS level can contribute to apoptosis in cancer cells (20).

Various forms of selenium, an essential trace element of the cell, have potent antitumor activity by inhibiting the proliferation of various types of cancer, including breast, prostate, lung, melanoma, and cervical cancers (21). Furthermore, there are studies reporting the use of inorganic selenium and synthetic selenium compounds along with gemcitabine, a chemotherapeutic agent used in PC, to increase the growth inhibition of PC cells (22). The effect of sodium selenite (NaSe) on PDAC is considered to be clinically relevant as it is more potent than the other drugs tested. NaSe exerts its anticarcinogenic activity by directly oxidizing cellular free thiols (23). Moro et al. (24) reported that NaSe is a promising candidate for the treatment of PDAC because it has a significant cytotoxic effect on PDAC without any damage to non-malignant tissue components.

The fact that most PC patients are diagnosed while they are in the process of metastasis points to the importance of therapeutically targeting the metastatic stages in particular. For this purpose, in our studies to date, it has been shown for the first time that juglone is an effective agent in the invasion, adhesion, and metastasis processes in PC cell lines (25,26). Investigation of the effects of juglone-selenium (J/S) combination on different molecules involved in invasion and metastasis is necessary to develop new juglone- and selenium-based strategies for the treatment of PC. In our previous study, we showed that J/S has a cytotoxic and dose-dependent suppressive effect on invasion and metastasis in PANC-1 and BxPC-3 cells (27).

In this study, the effects of J/S application on epithelial-mesenchymal transition, and migration properties in PC cells were investigated. For this purpose, the expression levels of *FOXL1*, *vimentin (VIM)* and *MMP-7* were examined. In addition, the effects of J/S on migration properties were evaluated by the wound healing method.

METHODS

Cell Culture

PANC-1 and BxPC-3 PC cell lines received from the American Type Culture Collection (Rockville, Md) were cultured according to the manufacturer's instructions. Cells were cultured in DMEM (Gibco, UK) and RPMI (Gibco, UK) medium, respectively, including 10% fetal bovine serum (FBS) (HyClone, Fisherscientific, Canada) and 1% penicillin/streptomycin (Gibco, UK) at 37 °C and 5% CO_2 juglone and NaSe were supplied commercially (Sigma-Aldrich Chemical Company, USA).

Determination of the Cytotoxic Effects of Juglone-selenium and MTT Assay

The MTT (reagent from Sigma-Aldrich, USA) assay used to determine the cytotoxic effects of J/S on human PC cells was performed as described in our previous study (27).

Wound-healing Assay

A wound-healing assay was used to evaluate the metastatic and proliferative behaviors of PC cells following J/S combination therapy. For this purpose, cells were seeded in 6-well cell culture plates to cover approximately 70-80% of the wells. Cells were cultured in DMEM or RPMI 1640 medium supplemented with 10% FBS and 1% penicillin/streptomycin for 24 hours (h). One day later, at cell seeding time, the cells were transferred to a starvation medium (starvation medium contains 0% FBS and 1% pen/strep). After 16 h of incubation in the starvation medium, the cells in the wells were scraped with a 200 µL pipette tip to make a straight-line wound. After scratching, the detached cells were washed by gently rinsing the well with PBS, and the determined J/S concentrations were added to the medium and incubated for 48 h in an atmosphere of 5% CO_2 at 37 °C. At least 4 repetitions were performed for each group. Wounds were visualized under a microscope at 0, 24, and 48 h.

Gene Expression Analysis

The effects of juglone application at 5, 10, 15, and 20 µM concentrations in the presence of 2,5 µM NaSe on the expression of *FOXL1*, *VIM*, and *MMP-7* genes were determined by quantitative real-time polymerase chain reaction (qPCR). RNA was isolated from all J/S-treated and control groups and translated into cDNA. Suitable primers for the targeted genes and for the β-actin gene, the housekeeping gene in our study, were used for qPCR.

Statistical Analysis

The $2^{-\Delta\Delta CT}$ method was used to analyze the relative changes in gene expression. Expression changes as 2-fold increase and decrease were considered significant. For the migration assay, the wound area was calculated using ImageJ software. The area comparison between the control and J/S combination-treated groups was done by imaging cells at 0, 24, and 48 h. Wound closure rates were calculated as a percentage by comparing the remaining areas after 24 h and 48 h.

Ethics Statement

This study was approved by the Local Ethical Committee of Selçuk University Faculty of Medicine (decision no: 2019/256, date: 16.10.2019) and conducted in accordance with the Declaration of Helsinki.

RESULTS

Cytotoxic Effects of Juglone-selenium

For PANC-1 and BxPC-3 cell lines, IC50 doses of J/S were determined as 16.3 µM and 15.17 µM for 24 h, respectively, using the GraphPad Prism 6 program by Arikoglu et al. (27). Based on these IC50 doses, the J/S treatment doses used in our experiments were 5, 10, 15 and 20 µM.

Wound-healing Assay

The effect of the J/S combination on the invasive ability was investigated using the wound healing assay. According to the wound healing assay, it was observed that migration was suppressed in both J/S-treated cell lines compared with the control group. The results of the wound healing assay are shown as percentage rates in Table 1 and as images in Figures 1 and 2. However, cell losses were also observed with suppression of migration in BxPC-3 cells (Figure 2). In microscopic evaluations, it was observed that these cell losses were not due to cell death; rather, cell loss was due to the loss of their adhesion properties, separating and disrupting tissue integrity.

Effect of Juglone-selenium Applications on Gene Expression

Gene expression analysis results related to the effects of the J/S combination on gene expression were shown in Figures 3 and 4. While evaluating the results, changes of two fold and above were considered significant. Following J/S treatment, the expression of *FOXL1*, *VIM*, and *MMP-7* genes was analyzed by qPCR. After 24 h of J/S treatment in the PANC-1 cell line, gene expression levels were determined and compared with the control group. *MMP-7* gene expression increased 2.7-fold, 8.2-fold, and 6.4-fold at 10, 15, and 20 µM J/S treatments, respectively; and *VIM* gene expression increased 2.3-fold, 3.3-fold, and 2.4-fold at 10, 15, and 20 µM doses, respectively, while *FOXL1* gene expression decreased 12.3-fold, 8-fold, 11.3-fold, and 4.6-fold in 5, 10, 15, and 20 µM treatments (Figure 3).

Table 1. Migration properties of PANC-1 and BxPC-3 cells and the percent closure rates of wound healing assay after J/S treatments (%)

	PANC-1		BXPC-1	
	24-hour	48-hour	24-hour	48-hour
Control	23.98	36.46	38.72	96.56
5 µM	28.17	45.14	-38.93	-34.56
10 µM	5.78	9.78	-16.77	-4.75
15 µM	12.08	14.21	-2.94	-16.80
20 µM	3.77	6.34	-6.23	-10.77

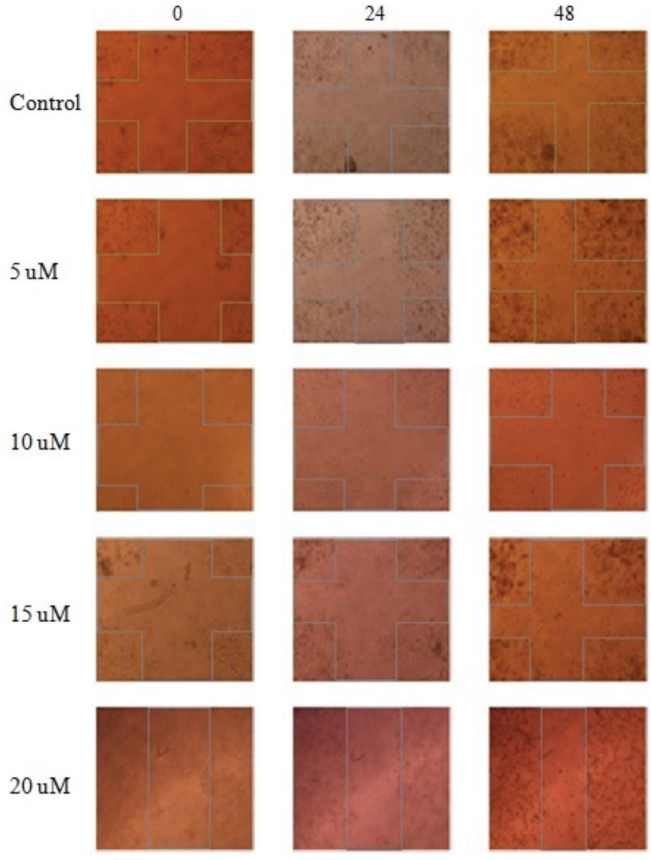

Figure 1. Microscopic images of the effects of J/S treatments on the migration properties of PANC-1 cells

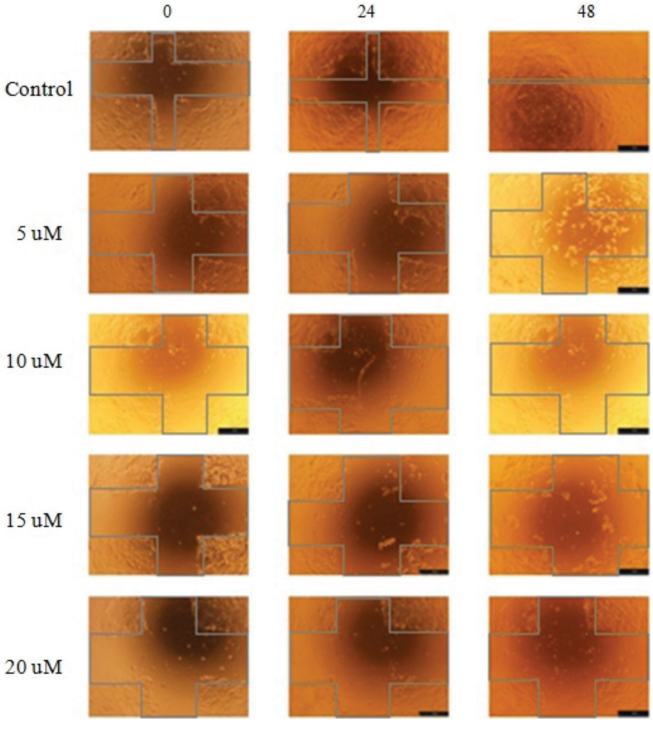

Figure 2. Microscopic images of the effects of J/S treatments on the migration properties of BxPC-3 cells

MMP-7 gene expression in BxPC-3 cells showed a 2.5-fold, 5.5-fold, 6.5-fold increase, and 3.2-fold decrease with 5, 10, 15, and 20 µM treatments, respectively. Unlike PANC-1 cells, after J/S treatment, *VIM* expression decreased at all doses with significant levels as 7.3-fold, 3.9-fold, 4.8-fold, and 6.9-fold, respectively. *FOXL1* gene expression decreased significantly at all doses as 8.5-fold, 3.3-fold, 3.8-fold and 6.6-fold decreases in 5, 10, 15 and 20 µM treatments, respectively, similar to that observed in PANC-1 cells (Figure 4).

DISCUSSION

Due to the late diagnosis, rapid development, and *de novo* chemoresistance of PC cells against cytotoxic chemotherapeutic agents and/or radiotherapy, difficulties arise for treating PC, leading to a high mortality rate (28). The interaction between cancer stem cells and TME in PC causes poor prognosis in patients with multifactorial chemoresistance (29). Despite the most frequently altered genes (*KRAS, TP53, CDKN2A,* and *SMAD4*) being determined in PC, limited recovery is observed due to the resistance to chemotherapy and radiotherapy as well as immune therapy, which leads to searches for new approaches to treat PC focusing on various phytochemicals (30-32).

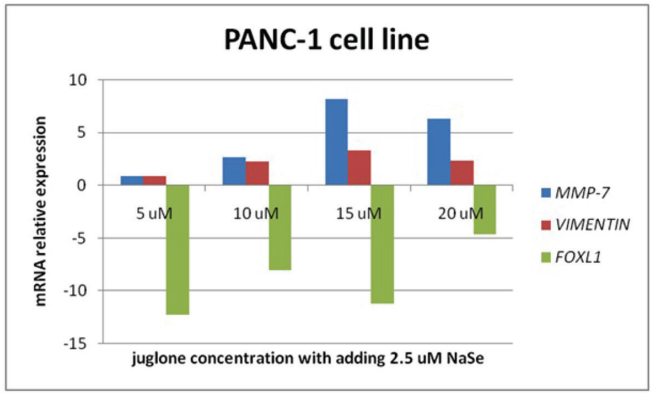

Figure 3. Effects of J/S treatments on the expressions of target genes in PANC-1 cells

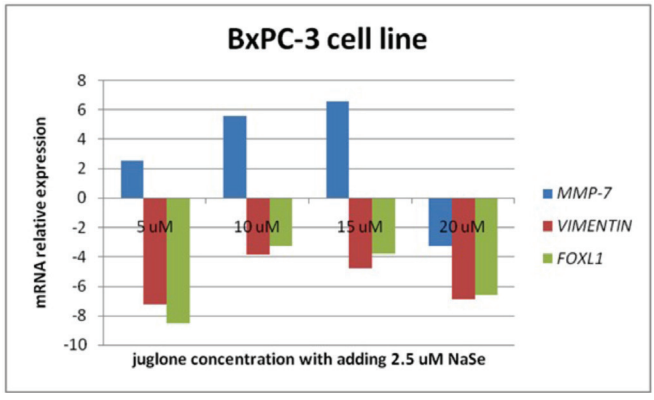

Figure 4. Effects of J/S treatments on the expressions of target genes in BxPC-3 cells

Juglone, a secondary metabolite obtained from various parts of Juglandaceae walnut trees, such as leaves, roots, shells, and fruits, is an effective cytotoxic agent that induces ROS and causes a change in redox homeostasis in the cell, leading to apoptosis as well as necrotic cell death. The cytotoxic effects of juglone on cancer cells have been demonstrated by several studies on different cancer cells such as human prostate cancer cells (LNCaP), human gastric cancer cells (SGC-7901), human leukemia cells (HL-60), and human colon carcinoma cells (HCT-8 and HCT-15) (33-37). Juglone is also an effective inhibitor of Pin1 (peptidyl-prolyl isomerase), which plays a role in cell cycle control and is overexpressed in most cancer types (38).

Selenium, an essential trace element, plays an important role in many basic physiological processes by participating in the structure of selenoproteins (39). To date, the therapeutic effects of organic and inorganic forms of selenium components on human cancers have been investigated (22,40-42). Selenium-containing compounds, which participate in basic biological processes ranging from apoptosis to immunity, including cellular antioxidant defense, DNA protection, and repair, also function as antioxidant enzymes such as thioredoxin reductase and glutathione peroxidase (41-42). Selenium has also been reported to have an anti-cancer effect by mechanisms such as accelerating oxidation in cancer cells, modulating carcinogenesis metabolism, regulating the Trx redox system and inhibiting angiogenesis, as well as inducing apoptosis secondary by creating ROS (40-42).

The results indicating that selenium inhibits invasion and metastasis in cancer cells also suggest that selenium is a promising chemotherapeutic agent for treating PC (41). It has been reported that high levels of selenium in the blood of patients who take dietary selenium supplements with PC significantly reduce the incidence and mortality of cancer and increase the DNA damage repair response (40,43). In a Phase I clinical trial evaluating the safety and efficacy of intravenously administered NaSe, it was found that NaSe can be safely tolerated in humans up to 10.2 mg/m (44). Moro et al. (24) revealed that 15 µM NaSe, which they determined as the application dose, is significantly below the maximum tolerated dose reported for humans. In addition, according to transcriptome data analysis, it decreases the expression of genes having metastatic potential (*CEMIP, DDR2, PLOD2, P4HA1*) known to drive PDAC growth. They reported that it significantly increased the expression of genes (*ATF3, ACHE*)

that induce cell death. In the same study, it was determined that NaSe has extraordinary efficacy and specificity against drug-resistant PC by reducing de novo tumor cell growth while protecting non-neoplastic tissues in an organotypic tissue culture model (24).

FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan) and gemcitabine/nab-paclitaxel combinations are commonly used as first-line systemic therapy for PDAC (14,15). Radiation therapy is recommended following the chemotherapeutic treatment of PCs, and new combinations are being investigated to enhance chemotherapeutics (45). Wooten et al. (22) showed that selenium has an antimetastatic effect by creating a synergistic effect with gemcitabine in their study on BxPC-3 cell lines grown on 2D and 3D platforms.

FOX proteins are a large family of transcription factors that have important functions in different biological processes such as cell cycle control, differentiation, epithelial proliferation, and development of the gastrointestinal tract (46,47). It has been hypothesized that low *FOXL1* expression is associated with an increase in cancer-related mortality and therefore affects PC progression. It has been reported that *FOXL1*, especially expressed in the gastrointestinal tract, is a tumor suppressor gene, and studies have shown that the expression of *FOXL1* leads to apoptosis of cancer cells by inducing *TRAIL* expression (48) and triggers apoptosis by disrupting mitochondrial transmembrance depolarization by inducing cytochrome c release (49). In osteosarcoma, overexpression of *FOXL1* has also been reported to suppress proliferation by increasing the expression of p27 and p21, thus stopping the cycle (49). In addition, *FOXL1* represses *ZEB1* transcription by binding directly to the promoter region, which is one of the activators of epithelial -mesenchymal changes that affect cancer cell invasion and aggressiveness (48).

Our previous study (27) reported that J/S has a cytotoxic and dose-dependent suppressive effect on invasion and metastasis in PANC-1 and BxPC-3 cells. Because the increase in *FOXL1* expression was shown in the literature to be associated with suppression of invasion and adhesion ability; an increase in *FOXL1* expression was expected after J/S application in our study. However, contrary to expectations, *FOXL1* expression decreased at all doses in both cell lines. Chen et al. (50) reported that higher *FOXL1* expression in gliomas is associated with a worse prognosis, unlike other malignant tumors. Our study suggests that the decrease in the expression level of *FOXL1* is important in PC, possibly because suppressing the expression of *FOXL1* by J/S may make the poor prognosis of PC more moderate.

EMT is a physiological process in which epithelial cells transform into mesenchymal phenotype cells through certain physiological procedures and under certain conditions. In the EMT process, the epithelial cell loses its characteristic cell-cell connections, polarity changes, keratin intercalation in the cytoskeletal system transforms into VIM intercalation, and becomes isolated from neighboring cells and mobile and anoikis-resistant cells (51). Apart from apoptosis, the most well-known mode of cell death has been anoikis and ferroptosis recently. Ferroptosis is an iron-dependent and non-apoptotic form of cell death that is commonly involved in human pathological conditions, including cancer therapy resistance and brain injury (52). Karki et al. (53) showed that juglone also induces cell death by ferroptosis in the *KRAS*-mutated MIA PaCa-2 pancreatic cell line. *VIM* is an important gene involved in the EMT and metastasis. According to our results, J/S administration increased *VIM* expression in PANC-1 cells and a significant decrease in BxPC-3 cells. This opposite effect of J/S may be because of the different origins and different cell properties and behaviors of the pancreatic cell lines. In addition, unexpected increases in *VIM* expression in PANC-1 cells after J/S application may be caused by different unknown functions of *VIM*.

Another key gene investigated in our study is the *MMP-7* gene, which is a matrix metalloprotease that plays an important role in invasion. MMP-7 is especially secreted from epithelial cells and is overexpressed in many types of cancer (54) including PC (55-57). Therefore, suppression of *MMP-7* expression may be an important strategy for inhibiting PC metastasis. Avcı et al. (25) showed that juglone has suppressive effects on *MMP-2* and *MMP-9* expression in PANC-1 and BxPC-3 pancreatic cells. In our study, it was determined that J/S did not have a suppressive effect on *MMP-7*. There was an increase in *MMP-7* expression in both cells at all doses, whereas there was a decrease in BxPC-3 cells only at the 20 μM dose. This result is almost consistent with the results of Gokturk et al. (26) who reported increased *MMP-7* expression in PANC-1 and BxPC3 cells. We suggest that the increase in the expression of the *MMP-7* gene caused by J/S may create an antimetastatic effect differently than we anticipated. Powell et al. (57) stated that juglone induces apoptosis because of increased expression of the *MMP-7* gene, caused by the production of membrane-bound FAS ligand and binding to the FAS receptor, which is the main mediator of epithelial cell apoptosis. Endothelial and epithelial cells can continue to survive and proliferate when in contact with the ECM. If this connection is broken, it can trigger anoikis both *in vitro* and *in vivo*. Therefore, it is possible that the increase in *MMP-7* gene expression, which is responsible for the degradation of important matrix

proteins such as collagen and fibronectin, may trigger anoikis, leading to tumor cell apoptosis.

According to the wound healing assay, migration was suppressed in both cell lines compared with the control group. Migration in PANC-1 cells decreased in a dose-dependent manner. Although migration of BxPC-3 cells was suppressed at all doses, it was evaluated that this dramatic decrease was because of cell death due to the toxicity of J/S treatment. In the adhesion tests performed in our previous study (27), it was determined that J/S treatment decreased the adhesion levels of PC cells in a dose-dependent manner, consistent with our current wound-healing results.

CONCLUSION

It has been shown in our previous studies that juglone has cytotoxic and antimetastatic effects on PANC-1 and BxPC-3 cells, and selenium strengthens the cytotoxic and antimetastatic properties by suppressing invasion and metastasis. In this study, we evaluated the effects of J/S treatment on adhesion and invasion by evaluating the expression of *FOXL1*, *VIM,* and *MMP-7*, which are critical genes for metastatic processes and wound healing analysis. The potent antimetastatic effects of juglone on PC cells have been demonstrated in our previous studies and this study. Selenium also strengthens these effects. When all these studies are evaluated together, juglone should be evaluated as an important therapeutic candidate, especially for the development of antimetastatic agents for treating PC, which is known to have silent progress and metastasis at the time of diagnosis. For a more comprehensive evaluation of the juglone and J/S combination, which clearly showed the antimetastatic effects with the invasion, adhesion, and wound healing tests, more other genes and their protein products that have a role in metastatic processes should be investigated.

ETHICS

Ethics Committee Approval: This study was approved by the Local Ethical Committee of Selçuk University Faculty of Medicine (decision no: 2019/256, date: 16.10.2019) and conducted in accordance with the Declaration of Helsinki.

Informed Consent: The study does not require patient consent.

Authorship Contributions

Concept: H.A., Design: D.E.K., Data Collection or Processing: F.G., F.B., Analysis or Interpretation: D.E.K., H.A., Literature Search: F.G., F.B., Interpretation: D.E.K., Technical Studies: F.G., Cell Culture: F.B., Critical Review: H.A., Writing: D.E.K., H.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by the Scientific Research Projects Coordinatorship of Selçuk University (Project no: 19401145).

REFERENCES

1. Hidalgo M, Cascinu S, Kleeff J, Labianca R, Löhr JM, Neoptolemos J, et al. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. Pancreatology 2015;15:8-18.
2. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol 2018;24:4846-61.
3. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21.
4. Wanebo HJ, Vezeridis MP. Pancreatic carcinoma in perspective. A continuing challenge. Cancer 1996;78(3 Suppl):580-91.
5. Evans DB, Lee JE, Pisters PW, Charnsangavej C, Ellis LM, Chiao PJ, et al. Advances in the diagnosis and treatment of adenocarcinoma of the pancreas. Cancer Treat Res 1997;90:109-25.
6. Poste G, Fidler IJ. The pathogenesis of cancer metastasis. Nature 1980;283:139-46.
7. Ren B, Cui M, Yang G, Wang H, Feng M, You L, et al. Tumor microenvironment participates in metastasis of pancreatic cancer. Mol Cancer 2018;17:108.
8. Stopa KB, Kusiak AA, Szopa MD, Ferdek PE, Jakubowska MA. Pancreatic Cancer and Its Microenvironment-Recent Advances and Current Controversies. Int J Mol Sci 2020;21:3218.
9. Neesse A, Algül H, Tuveson DA, Gress TM. Stromal biology and therapy in pancreatic cancer: a changing paradigm. Gut 2015;64:1476-84.
10. Erkan M, Kurtoglu M, Kleeff J. The role of hypoxia in pancreatic cancer: a potential therapeutic target? Expert Rev Gastroenterol Hepatol 2016;10:301-16.
11. Lygidakis NJ, Jain S, Sacchi M, Vrachnos P. Adenocarcinoma of the pancreas--past, present and future. Hepatogastroenterology 2005;52:1281-92.
12. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, et al. Pancreatic cancer. Nat Rev Dis Primers 2016;2:16022.
13. Neoptolemos JP, Kleeff J, Michl P, Costello E, Greenhalf W, Palmer DH. Therapeutic developments in pancreatic cancer: current and future perspectives. Nat Rev Gastroenterol Hepatol 2018;15:333-48.
14. Kosuge T, Kiuchi T, Mukai K, Kakizoe T; Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP). A multicenter randomized controlled trial to evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. Jpn J Clin Oncol 2006;36:159-65.
15. Khorana AA, McKernin SE, Berlin J, Hong TS, Maitra A, Moravek C, et al. Potentially Curable Pancreatic Adenocarcinoma: ASCO Clinical Practice Guideline Update. J Clin Oncol 2019;37:2082-8.
16. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
17. Tempero MA, Malafa MP, Chiorean EG, Czito B, Scaife C, Narang AK, et al. Pancreatic Adenocarcinoma, Version 1.2019. J Natl Compr Canc Netw 2019;17:202-10.
18. de Geus SWL, Sachs TE. A Paradigm Shifts: Neoadjuvant Therapy for Clearly Resectable Pancreatic Cancer .Ann Surg Oncol 2023;75:1481-96
19. Narayanan P, Farghadani R, Nyamathulla S, Rajarajeswaran J, Thirugnanasampandan R, Bhuwaneswari G. Natural quinones induce ROS-mediated apoptosis and inhibit cell migration in PANC-1 human pancreatic cancer cell line. J Biochem Mol Toxicol 2022;36:e23008.

20. Jha BK, Jung HJ, Seo I, Suh SI, Suh MH, Baek WK. Juglone induces cell death of Acanthamoeba through increased production of reactive oxygen species. Exp Parasitol 2015;159:100-6.
21. Vinceti M, Filippini T, Del Giovane C, Dennert G, Zwahlen M, Brinkman M, et al. Selenium for preventing cancer. Cochrane Database Syst Rev 2018;1:CD005195
22. Wooten DJ, Sinha I, Sinha R. Selenium Induces Pancreatic Cancer Cell Death Alone and in Combination with Gemcitabine. Biomedicines 2022;10:149.
23. Jackson MI, Combs GF Jr. Selenium and anticarcinogenesis: underlying mechanisms. Curr Opin Clin Nutr Metab Care 2008;11:718-26.
24. Moro CF, Selvam AK, Ghaderi M, Pimenoff VN, Gerling M, Bozóky B, et al. Drug-induced tumor-specific cytotoxicity in a whole tissue *ex vivo* model of human pancreatic ductal adenocarcinoma. Front Oncol 2022;12:965182.
25. Avcı E, Arıkoğlu H, Erkoç Kaya D. Investigation of juglone effects on metastasis and angiogenesis in pancreatic cancer cells. Gene 2016;588:74-8.
26. Gokturk F, Erkoc-Kaya D, Arikoglu H. Juglone can inhibit angiogenesis and metastasis in pancreatic cancer cells by targeting Wnt/β-catenin signaling. Bratisl Lek Listy 2021;122:132-7.
27. Arikoglu H, Dursunoglu D, Kaya DE, Avci E. The effects of Juglone-Selenium combination on invasion and metastasis in pancreatic cancer cell lines. Afr Health Sci 2022;22:334-42.
28. Schneider G, Siveke JT, Eckel F, Schmid RM. Pancreatic cancer: basic and clinical aspects. Gastroenterology 2005;128:1606-25.
29. Zeng S, Pöttler M, Lan B, Grützmann R, Pilarsky C, Yang H. Chemoresistance in Pancreatic Cancer. Int J Mol Sci 2019;20:4504.
30. Deng S, Shanmugam MK, Kumar AP, Yap CT, Sethi G, Bishayee A. Targeting autophagy using natural compounds for cancer prevention and therapy. Cancer 2019;125:1228-46.
31. Piffoux M, Eriau E, Cassier PA. Autophagy as a therapeutic target in pancreatic cancer. Br J Cancer 2021;124:333-44.
32. Santofimia-Castaño P, Iovanna J. Combating pancreatic cancer chemoresistance by triggering multiple cell death pathways. Pancreatology 2021;21:522-9
33. Kamei H, Koide T, Kojima T, Hashimoto Y, Hasegawa M. Inhibition of cell growth in culture by quinones. Cancer Biother Radiopharm 1998;13:185-8.
34. Xu HL, Yu XF, Qu SC, Zhang R, Qu XR, Chen YP, et al. Anti-proliferative effect of Juglone from Juglans mandshurica Maxim on human leukemia cell HL-60 by inducing apoptosis through the mitochondria-dependent pathway. Eur J Pharmacol 2010;645:14-22.
35. Ji YB, Qu ZY, Zou X. Juglone-induced apoptosis in human gastric cancer SGC-7901 cells via the mitochondrial pathway. Exp Toxicol Pathol 2011;63:69-78.
36. Xu H, Yu X, Qu S, Sui D. Juglone, isolated from Juglans mandshurica Maxim, induces apoptosis via down-regulation of AR expression in human prostate cancer LNCaP cells. Bioorg Med Chem Lett 2013;23:3631-4.
37. Yang L. Effects of Juglone on Adhesion and Activities of Matrix Metalloproteinases in Human Colon Carcinoma HCT-8Cells 2012.
38. Fila C, Metz C, van der Sluijs P. Juglone inactivates cysteine-rich proteins required for progression through mitosis. J Biol Chem 2008;283:21714-24.
39. Bartolini D, Sancineto L, Fabro de Bem A, Tew KD, Santi C, Radi R, et al. Selenocompounds in Cancer Therapy: An Overview. Adv Cancer Res 2017;136:259-302.
40. Chatterjee S, Combs GF Jr, Chattopadhyay A, Stolzenberg-Solomon R. Serum selenium and pancreatic cancer: a prospective study in the Prostate, Lung, Colorectal and Ovarian Cancer Trial cohort. Cancer Causes Control 2019;30:457-64.
41. de Rosa V, Erkekoğlu P, Forestier A, Favier A, Hincal F, Diamond AM, et al. Low doses of selenium specifically stimulate the repair of oxidative DNA damage in LNCaP prostate cancer cells. Free Radic Res 2012;46:105-16.
42. Kim TS, Yun BY, Kim IY. Induction of the mitochondrial permeability transition by selenium compounds mediated by oxidation of the protein thiol groups and generation of the superoxide. Biochem Pharmacol 2003;66:2301-11.
43. Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA 1996;276:1957-63.
44. Brodin O, Eksborg S, Wallenberg M, Asker-Hagelberg C, Larsen EH, Mohlkert D, et al. Pharmacokinetics and Toxicity of Sodium Selenite in the Treatment of Patients with Carcinoma in a Phase I Clinical Trial: The SECAR Study. Nutrients 2015;7:4978-94.
45. Leroux C, Konstantinidou G. Targeted Therapies for Pancreatic Cancer: Overview of Current Treatments and New Opportunities for Personalized Oncology. Cancers (Basel) 2021;13:799.
46. Perreault N, Sackett SD, Katz JP, Furth EE, Kaestner KH. Foxl1 is a mesenchymal Modifier of Min in carcinogenesis of stomach and colon. Genes Dev 2005;19:311-5.
47. Qin Y, Gong W, Zhang M, Wang J, Tang Z, Quan Z. Forkhead box L1 is frequently downregulated in gallbladder cancer and inhibits cell growth through apoptosis induction by mitochondrial dysfunction. PLoS One 2014;9:e102084.
48. Zhang G, He P, Gaedcke J, Ghadimi BM, Ried T, Yfantis HG, et al. FOXL1, a novel candidate tumor suppressor, inhibits tumor aggressiveness and predicts outcome in human pancreatic cancer. Cancer Res 2013;73:5416-25.
49. Chen X, Deng M, Ma L, Zhou J, Xiao Y, Zhou X, et al. Inhibitory effects of forkhead box L1 gene on osteosarcoma growth through the induction of cell cycle arrest and apoptosis. Oncol Rep 2015;34:265-71.
50. Chen A, Zhong L, Lv J. FOXL1 overexpression is associated with poor outcome in patients with glioma. Oncol Lett 2019;18:751-7.
51. Klymkowsky MW, Savagner P. Epithelial-mesenchymal transition: a cancer researcher's conceptual friend and foe. Am J Pathol 2009;174:1588-93.
52. Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, et al. Ferroptosis: past, present and future. Cell Death Dis 2020;11:88.
53. Karki N, Aggarwal S, Laine RA, Greenway F, Losso JN. Cytotoxicity of juglone and thymoquinone against pancreatic cancer cells. Chem Biol Interact 2020;327:109142.
54. Yamamoto H, Itoh F, Iku S, Adachi Y, Fukushima H, Sasaki S, et al. Expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human pancreatic adenocarcinomas: clinicopathologic and prognostic significance of matrilysin expression. J Clin Oncol 2001;19:1118-27.
55. Zeng ZS, Shu WP, Cohen AM, Guillem JG. Matrix metalloproteinase-7 expression in colorectal cancer liver metastases: evidence for involvement of MMP-7 activation in human cancer metastases. Clin Cancer Res 2002;8:144-8.
56. Polistena A, Cucina A, Dinicola S, Stene C, Cavallaro G, Ciardi A, et al. MMP7 expression in colorectal tumours of different stages. In Vivo 2014;28:105-10.
57. Powell WC, Fingleton B, Wilson CL, Boothby M, Matrisian LM. The metalloproteinase matrilysin proteolytically generates active soluble Fas ligand and potentiates epithelial cell apoptosis. Curr Biol 1999;9:1441-7.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:256-262
DOI: 10.4274/BMJ.galenos.2023.2023.3-19

Research

Differentiating Renal Cell Carcinoma and Minimal Fat Angiomyolipoma with Volumetric MRI Histogram Analysis

Renal Hücreli Karsinom ve Minimal Yağ Anjiyomiyolipomunun Volümetrik MRG Histogram Analizi ile Ayrımı

Özlem Akıncı, Furkan Türkoğlu, Mustafa Orhan Nalbant, Ercan İnci

University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Radiology, İstanbul, Türkiye

ABSTRACT

Objective: In this study, the utility of histogram parameters derived from diffusion-weighted imaging to differentiate renal cell carcinoma (RCC) from renal minimal fat angiomyolipoma (MFAML) was investigated.

Methods: In this retrospective study, 98 patients who were histopathologically diagnosed with RCC and MFAML and who underwent magnetic resonance imaging (MRI) examinations between 2015 and 2022 were included. Demographic data, preoperative MRI findings, MRI apparent diffusion coefficient (ADC) histogram analyses, operation types, and postoperative histopathological data of the patients were recorded. The mean, minimum (min), maximum (max), 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles as well as skewness, kurtosis, and variance of ADC values were calculated.

Results: The study included 61 males and 37 females. Eighty eight of the patients had RCC and 10 had AML. In terms of age and gender, there was no significant difference between the two groups. The AML group's ADCmin, ADCmedian, ADCmean, ADCmax, 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles were all lower than those of the RCC group. ADCmax value ($p<0.001$), as well as ADCmedian and the 50th, 75th, 90th, and 95th percentiles of ADC values ($p<0.05$), demonstrated a statistically significant difference. However, there was no statistical significance between ADCmin, ADCmean, and the 5th, 10th, and 25th percentiles of ADC values ($p>0.05$). The area under the curve, sensitivity, and specificity of the ADCmax value were 0.795, 62.4%, and 88.9%, respectively.

Conclusion: A whole tumor histogram and textural analysis of ADC values could be useful in distinguishing MFAML from RCC.

Keywords: Renal cell carcinoma, renal angiomyolipoma, magnetic resonance imaging, diffusion weighted imaging, histogram analysis

ÖZ

Amaç: Bu çalışmada, difüzyon ağırlıklı görüntülemeden elde edilen histogram parametrelerinin, renal hücreli karsinomu (RHK) renal minimal yağ anjiyomiyolipomdan (MYAML) ayırt etmede etkinliği araştırıldı.

Gereç ve Yöntem: Bu retrospektif çalışmaya histopatolojik olarak RHK ve MYAML tanısı alan ve 2015 ve 2022 yılları arasında manyetik rezonans görüntülemesi (MRG) yapılan 98 hasta dahil edildi. Hastaların demografik verileri, preoperatif MRG bulguları, MRG görünür difüzyon katsayısı (ADC) histogram analizleri, operasyon tipleri, postoperatif histopatolojik verileri kaydedildi. Ortalama, minimum (min), maksimum (maks), medyan 5., 10., 25., 50., 75., 90. ve 95. yüzdelikleri içeren ADC değerlerinin histogram parametreleri ile çarpıklık, basıklık ve varyansı hesaplandı.

Bulgular: Çalışmaya 61 erkek ve 37 kadın dahil edildi. Hastaların 88'i RHK idi ve 10'u MYAML idi. İki grup arasında yaş ve cinsiyet açısından anlamlı fark yoktu. MYAML grubunun ADCmin, ADCmedyan, ADCortalama, ADCmaks, 5., 10., 25., 50., 75., 90. ve 95. yüzdeliklerinin tümü RHK grubundan düşüktü. ADCmaks değeri ($p<0,001$) ile ADCmedyan ve ADC değerlerinin 50., 75., 90. ve 95. yüzdelikleri ($p<0,05$) istatistiksel olarak anlamlı fark gösterdi. Bununla birlikte, ADCmin, ADCortalama ve ADC değerlerinin 5., 10. ve 25. yüzdelikleri arasında istatistiksel anlamlı fark yoktu ($p>0,05$). ADCmaks değerinin eğri altındaki alanı, duyarlılık ve özgüllüğü sırasıyla 0,795, %62,4 ve %88,9 idi.

Sonuç: Tüm tümör histogramı ve ADC değerlerinin doku analizi, MYAML'yi RHK'den ayırt etmede yararlı olabilir.

Anahtar Kelimeler: Renal hücreli karsinom, renal anjiyomiyolipom, manyetik rezonans görüntüleme, difüzyon ağırlıklı görüntüleme, histogram analizi

Address for Correspondence: Özlem Akıncı, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Radiology, İstanbul, Türkiye
Phone: +90 505 628 25 28 E-mail: dr.ozlemgungor@yahoo.com ORCID ID: orcid.org/0000-0002-6615-4892

Cite as: Akıncı Ö, Türkoğlu F, Nalbant MO, İnci E. Differentiating Renal Cell Carcinoma and Minimal Fat Angiomyolipoma with Volumetric MRI Histogram Analysis. Med J Bakirkoy 2023;19:256-262

Received: 11.04.2023
Accepted: 04.06.2023

INTRODUCTION

Renal angiomyolipoma (AML) is a benign kidney tumor that can contain a variety of cell types, including blood vessels, smooth muscle cells, and adipose tissue (1). Because of their macroscopic fat, most AML can be easily identified on computed tomography or magnetic resonance imaging (MRI), but only around 5% of AML can be observed on imaging without any visible fat [minimal fat AML (MFAML)] (2,3). It is vital to differentiate AML from renal cell carcinoma (RCC) because AML, particularly when it is tiny and asymptomatic, can be monitored without any therapy, but RCC often requires surgical excision (4). Despite different MRI characteristics, MFAML may be difficult to distinguish from other renal malignant tumors, particularly clear cell renal cell carcinoma (ccRCC), which accounts for 75% of all RCCs in adults (5). Diffusion-weighted imaging (DWI) has been shown to be beneficial for the functional assessment of renal malignancies. This makes it possible to characterize tumors in a noninvasive manner (6-8).

DWI apparent diffusion coefficient (ADC) can indicate tissue water molecular diffusion and distinguish benign from malignant kidney lesions. Most earlier research evaluated ADC values using manually defined regions of interest (ROIs) on the tumor's largest practical section, which did not accurately reflect its diffusion characteristics (9,10).

The volumetric ADC histogram of the entire lesion was used to assess ADC values across the lesion without ROI placement to ensure repeatability and calculation accuracy. Histogram analysis is a statistical tool for assessing the properties of all vowels in an ROI to better estimate the tumor biological characteristics and histological heterogeneity (11). By recording the ADC values throughout the whole tumor, this technique can remove sampling bias.

The utility of DWI histogram analysis in the differential diagnosis of RCC and MFAML has been investigated in a very limited amount of published studies. The aim of this study was to investigate the ability of the ADC histogram and textural analysis to distinguish between MFAML and RCC.

METHODS

This retrospective study included 98 patients who were diagnosed with RCC and AML during postoperative histopathological examination between January 2015 and December 2022 and who had pre-operative MRI images. An approval from an University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee was obtained for the study (decision no: 2023-01-15, date: 09.01.2023). Patients who were histopathologically diagnosed with RCC and AML, did not receive radiotherapy or chemotherapy before surgery, did not contain macroscopic fat, and did not have motion artifacts that would impair image quality were included in the study.

Patients who had no preoperative MRI (n=10), had typical findings of AML on conventional MRI (n=8), were getting cancer treatment before an MRI exam (n=15), had imaging artifacts that make diagnosing lesions more difficult (n=10), had an interval between surgery and an MRI examination longer than one month (n=17), had a pathological diagnosis other than RCC or AML (n=8), or had undergone kidney surgery in the past for any reason (n=7) were excluded from the study. There were 75 patients excluded. Our study included 98 patients, 88 of whom had RCC and 10 of whom had AML. In the calculation made for the power analysis carried out with the G Power 3.1.9.7 (Franz Faul, Germany) program, it was assumed that the effect size would be d=1.205. In the calculation made with the determined effect size and a 5% margin of error, the strength of the study was found to be 86.9%.

Demographic data, preoperative MRI findings, MRI ADC histogram analyses, operation types, and postoperative histopathological data of the patients were recorded. Data from MRI ADC histograms were compared between the groups.

On a 3.0 T magnetic resonance system, a 16-channel phased array surface coil was used to receive the signal (Siemens Medical Solutions, Erlagen, Germany). DWI was administered at b-values of 1000 s/mm^2. The minimum (min) fasting time required before an MRI is four hours. Transverse, sagittal, and coronal thin-section turbo spin-echo T2-weighted images were acquired (20 slices; thickness: 3 mm with no intersection gap (IG); TR/TE: 5800/100 ms; number of signals acquired: 2; resolution: 0.8 mm 0.8 mm). The axial images at b values of 1000 s/mm^2 were acquired with respiratory-triggered single-shot echo-planar sequences [matrix, 160x192; field of view, 36-44 cm; slice thickness, 4 mm; IG, 1 mm; bandwidth (kHz/pixel), 250; acquisition time (ms) 4-5; flip angle (degrees) 90; number of excitations (NEX), 6].

Image Analysis

All of the raw data from the DWI was transferred to a personal computer using the picture archiving and communication system, where it was then processed using the voxel program LIFEx 7.2.0, (https://lifesoft.org) which is free and open source. All MR scans were independently

reviewed by two radiologists (8 years of experience each in abdominal MRI) who were blinded to the clinical data and histopathologic findings. The axial T2-weighted images were used as a guide to manually draw the ROI encompassing the lesion in each segment. Automatically, the data from each ROI was combined into a volumetric ROI that described the entire tumor in voxels (Figure 1, 2). The following model was then used to create a volumetric ADC map: Diffusion-induced signal attenuation is denoted by S = S0 exp(b ADC), where S0 is the signal intensity without diffusion sensitization and b is the value that sets the level of diffusion weighting in the signal. The min, maximum (max), skewness and variance of ADC values as well as the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles were determined. The point on the left where n% of the voxel values from that histogram were observed was the nth percentile. Positive skewness, which reflects the deviation of the distribution median from the mean value, indicates that the right tail

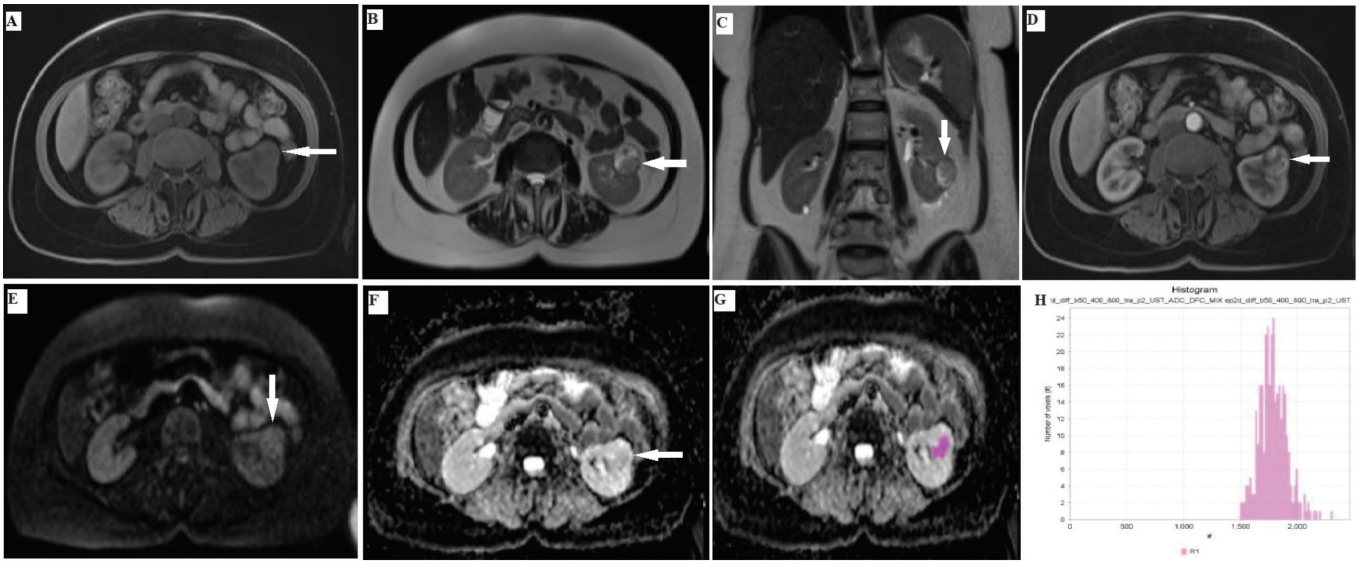

Figure 1. Clear cell renal cell carcinoma in a 65-year-old woman. (A) The axial T1-weighted fat suppression image of the lesion exhibits a low signal intensity; (B) On the axial T2-weighted image, the lesion has a high signal intensity; (C) On the coronal T2-weighted image, the lesion exhibits strong signal intensity; (D) On the axial T1-weighted post contrast fat supression image, the lesion exhibits strong contrast enhancement; (E) Diffusion-weighted imaging reveals concrete restricted diffusion around the lesion; (F) Lesion shows low apparent diffusion coefficient (ADC) on ADC; (G) Lesion color ADC map, freehand region of interest schematic; (H) ADC value was concentrated on the right side of the histogram, as shown by the corresponding volumetric histogram

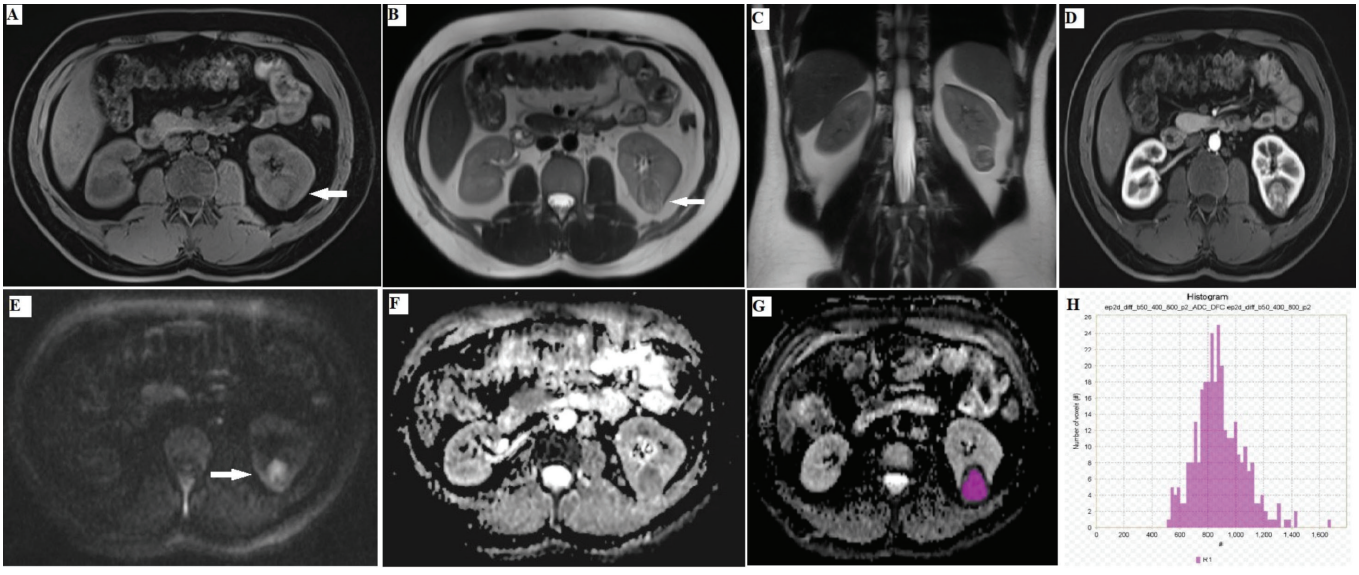

Figure 2. Angiomyolipoma of the kidney in a 55-year-old woman. (A) The axial T1-weighted fat suppression image of the lesion exhibits a low signal intensity; (B) On the axial T2-weighted image, the lesion has a high signal intensity; (C) On the coronal T2-weighted image, the lesion exhibits strong signal intensity; (D) On the axial T1-weighted post contrast fat supression image, the lesion exhibits a slight contrast enhancement; (E) Diffusion-weighted imaging reveals concrete restricted diffusion around the lesion; (F) Lesion displays low apparent diffusion coefficient (ADC); (G) Lesion color ADC map, freehand region of interest schematic, and diffusion image; (H) ADC value was concentrated on the middle and left of the volumetric histogram, according to the corresponding histogram

of the distribution is flatter or longer than the left tail. The peakiness of the histogram distribution is reflected by kurtosis. High kurtosis distributions have heavy tails, a sharp peak close to the mean, and a rapid decline.

Statistical Analysis

Statistical analysis was performed using IBM SPSS 23.0 (Chicago, IL, United States). Using the data set created by integrating the ADC measurements of each patient in the RCC and AML groups, histograms of the groups were generated. All patient measurements displayed a distributional variance, as indicated by the histograms. Using these measurements, descriptive statistics such as mean, min, median, max, standard deviation, skewness, kurtosis, and percentiles were computed for each patient group, and changes in these descriptive statistics were graphically displayed. The calculation of these group statistics relied on individuals. Using the t-test for independent samples, it was determined whether the statistics produced by individuals varied between groups. On the basis of individual data, receiver operating characteristic (ROC) curves were generated and a threshold value was determined for the compiled statistics. Sensitivity and specificity values were calculated for threshold values.

RESULTS

Demographic Data

In the study, 61 males and 37 females were included (Table 1). Eighty eight of the patients were RCC and 10 were MFAML. There was no significant difference between the two groups in terms of age and gender (respectively; p=0.099, and p=0.006).

Results of ADC Histogram Parameters

All of the ADC percentiles, including the min, median, mean, and max values, as well as the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles, were lower for the AML group than they were for the RCC group (Table 2). ADCmax value (p<0.001), as well as ADCmedian and the 50th, 75th, 90th,

Table 1. Demographic, radiological and pathological data of patients

	RCC n (%)/mean ± SD	MFAML n (%)/mean ± SD	p-value
Age	56.22±12.56	49.5±12.05	0.099[a]
Sex (male/female)	59 (67.0)/29 (33.0)	2 (20.0)/8 (80.0)	**0.006**[b]
Tumor diameter (mm)	54.89±32.92	47.3±41.92	0.228[a]

[a]Mann-Whitney U test, [b]Chi-square test. RCC: Renal cell carcinoma, MFAML: Minimal fat angiomyolipoma, SD: Standard deviation

Table 2. Comparisons of ADC histogram parameters between RCC and AML

ADC (10^{-3} mm^2/s)	RCC	AML	Total	p-value	Significance level
Mean	1.295±0.410	1.089±0.215	1.274±0.398	0.051	-
Standard deviation	0.246±0.133	0.162±0.083	0.238±0.131	**0.015**	95%
Median	1.303±0.427	1.081±0.218	1.281±0.416	**0.050**	95%
Minimum	0.609±0.482	0.751±0.260	0.624±0.465	0.196	-
Maximum	1.987±0.618	1.490±0.272	1.936±0.610	**0.003**	99%
Skewness	-0.1±0.6	0.3±0.3	0.0±0.6	**0.041**	95%
Kurtosis	0.7±1.5	-0.4±0.5	0.6±1.4	**0.007**	99%
5th	0.860±0.407	0.838±0.208	0.858±0.391	0.833	-
10th	0.985±0.388	0.879±0.2	0.974±0.374	0.291	-
25th	1.145±0.394	0.962±0.194	1.127±0.382	0.087	-
50th	1.303±0.427	1.081±0.218	1.281±0.416	**0.050**	95%
75th	1.450±0.447	1.207±0.248	1.425±0.436	**0.036**	95%
90th	1.597±0.480	1.321±0.285	1.569±0.471	**0.026**	95%
95th	1.685±0.504	1.354±0.309	1.653±0.497	**0.019**	95%

ADC: Apparent diffusion coefficient, RCC: Renal cell carcinoma, AML: Angiomyolipoma

and 95th percentiles of ADC values ($p<0.05$), demonstrated a statistically significant difference. However, there was no statistical significance between ADCmin, ADCmean, and the 5th, 10th, and 25th percentiles of ADC values ($p>0.05$). The RCC group had higher variance, skewness, and kurtosis than the AML group ($p<0.05$).

Diagnostic Performance

The ROC curve demonstrated the efficacy of ADC histogram parameters in the diagnosis of RCC; the ADCmax value had the highest area under the curve (AUC) (0.795), and the sensitivity and specificity under the threshold value of $1.794x10^{3}$ mm^2/s were 62.4% and 88.9%, respectively. The effectiveness of the diagnostic procedure was then followed by kurtosis. Under the threshold of 0.0, the sensitivity and specificity were respectively 61.2% and 77.8%. The AUC was greater than the value of the ADC at the 95th percentile of its distribution (0.738). Under the cut-off value of $1.594x10^{-3}$ mm^2/s, the sensitivity and specificity were 57.6% and 77.8%. The AUC was 0.727 which corresponded to the 90th percentile of the ADC value. Under the cut-off value of $1.611x10^{-3}$ mm^2/s, the sensitivity and specificity were 54.1% and 88.9% (Table 3).

The variance and the 75th percentile of the ADC value both contributed to a higher AUC (AUC =0.715). Under the threshold values of 0.181 and $1.445x10^{-3}$ mm^2/s, the sensitivity and specificity were 68.2% and 77.8% and 56.5% and 88.9%, respectively. The AUC was also higher with the ADCmedian and 50th percentile of the ADC value (AUC =0.708). With the cut-off value of $1.219x10^{-3}$ mm^2/s, the sensitivity and specificity were 58.8% and 77.8% for both parameters (Table 3).

DISCUSSION

Before surgical treatment, MFAML is frequently misdiagnosed as RCC (12). It is difficult but necessary for treatment planning and prognosis evaluation to distinguish between these two conditions (13). Histopathology is the gold standard in the differential diagnosis of MFAML and RCC. MFAML and RCC have similar imaging characteristics, which makes the differentiating diagnosis by traditional imaging modalities challenging (14). Most prior research used various DWI approaches to differentiate renal neoplasms due to the limited information identified by conventional MRI. According to a meta-analysis by Tordjman et al. (15), ADC of renal tumors that exclude cystic and necrotic areas has a greater ability to distinguish RCC from other renal lesions than whole-lesion ADC. According

Table 3. ROC results of ADC metrics histogram parameters

Test result variable(s)	AUC	Standard error[a]	Asymptotic sig.[b]	Asymptotic 95% confidence interval				
				Lower Bound	Upper Bound	Cut-off	Sensitivity	Specificity
Mean	0.708	0.062	0.040	0.586	0.831	1.267	0.565	0.889
Standard deviation	0.715	0.093	**0.035**	0.533	0.897	0.181	0.682	0.778
Median	0.708	0.063	**0.040**	0.585	0.832	1.219	0.588	0.778
Minimum	0.618	0.066	0.245	0.252	0.511	0.851	0.294	0.889
Maximum	0.795	0.058	**0.004**	0.681	0.908	1.794	0.624	0.889
Skewness	0.690	0.068	**0.062**	0.176	0.443	0.4	0.212	0.778
Kurtosis	0.748	0.073	**0.015**	0.606	0.891	0.0	0.612	0.778
5th	0.544	0.065	0.667	0.416	0.672	0.929	0.424	0.889
10th	0.633	0.067	0.192	0.502	0.763	1.001	0.494	0.889
25th	0.693	0.060	0.058	0.575	0.811	1.089	0.553	0.889
50th	0.708	0.063	**0.040**	0.585	0.832	1.219	0.588	0.778
75th	0.715	0.065	**0.035**	0.588	0.842	1.445	0.565	0.889
90th	0.727	0.071	**0.026**	0.588	0.865	1.611	0.541	0.889
95th	0.738	0.071	**0.019**	0.598	0.878	1.594	0.576	0.778

The test result variable(s): Kurtosis, p75, p95 has at least one tie between the positive actual state group and the negative actual state group.
[a] Under the nonparametric assumption
[b] Null hypothesis: true area =0.5
ROC: Receiver operating characteristic, ADC: Apparent diffusion coefficient, AUC: Area under the curve

to Li et al. (9), the whole tumor quantitative ADC histogram may be useful in differentiating between MFAML and RCC. According to the findings of our research, the ADCmin, ADCmedian, ADCmean, ADCmax, 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles were all lower for the AML group than they were for the RCC group. This finding is consistent with the findings of other studies published in the literature. A statistically significant difference was found between the ADCmax value ($p<0.001$) and the ADCmedian value, as well as the 50th, 75th, 90th, and 95th percentiles of the ADC values ($p<0.05$). It was hypothesized that the more limited water molecule transport in MFAML caused the lower ADC, and this hypothesis was in line with the findings of other investigations. One explanation is that the presence of adipose tissue and smooth muscle cells restricts the transport of water molecules (14). Since the adipose tissue contains very little water, even a small percentage of fat in MFAML can significantly lower the ADC value.

The asymmetry of the histogram is referred to as skewness (16,17). ADC texture analysis of ccRCC can provide a noninvasive method for accurately detecting high-staged tumors on preoperative imaging, as found by Kierans et al. (18), who found that ccRCC where in skewness based on ADC maps was much greater in high-staged tumors than in low-staged tumors. Our research showed that MFAML had much higher skewness than ccRCC. It showed that most MFAML ADC values were clustered to the left of the histogram in the low ADC values region, whereas most ccRCC ADC values were clustered to the right of the histogram in the high ADC values area. Due to the varying proportions of smooth muscle cells, adipose tissue, and tortuous blood arteries, the ADC value distribution was asymmetric and the skewness tended to be positive in MFAML, whereas in ccRCC, the ADC value was more concentrated and probably normal.

In our study, the AUC for distinguishing MFAML from ccRCC was higher with the 75th percentile ADC with the mean ADC. It was suggested that the higher percentile of the ADC value may be more representative for discriminating MFAML and ccRCC than the lower percentiles, which is consistent with a finding that is very similar to this one made by Tanaka et al. (7). This may be explained by the fact that the tiny necrotic components or cystic cavities of the malignant kidney tumor raise the ADC levels. As a result, the ADC value in the upper percentile may have better sensitivity and specificity.

Our research included several limitations and strengths. First, a limited number of people participated in the research. Second, because this was a retrospective study, there were naturally occurring biases in the selection of patients. Our use of whole-tumor ROI, which boasts superior reproducibility to single-slice ROI, was one of the key factors that contributed to the success of our research.

CONCLUSION

Our research showed that a whole tumor histogram and textural analysis of ADC values could be useful in distinguishing MFAML from RCC. It can increase the diagnostic accuracy and contribute to the process of determining an effective treatment approach.

ETHICS

Ethics Committee Approval: An approval from an University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee was obtained for the study (decision no: 2023-01-15, date: 09.01.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: Ö.A., E.İ., Design: Ö.A., E.İ., Data Collection or Processing: Ö.A., F.T., M.O.N., Analysis or Interpretation: Ö.A., F.T., M.O.N., E.İ., Literature Search: Ö.A., F.T., M.O.N., Writing: Ö.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Katabathina VS, Vikram R, Nagar AM, Tamboli P, Menias CO, Prasad SR. Mesenchymal neoplasms of the kidney in adults: imaging spectrum with radiologic-pathologic correlation. Radiographics 2010;30:1525-40.
2. Kim JK, Park SY, Shon JH, Cho KS. Angiomyolipoma with minimal fat: differentiation from renal cell carcinoma at biphasic helical CT. Radiology 2004;230:677-84.
3. Kim JK, Kim SH, Jang YJ, Ahn H, Kim CS, Park H, et al. Renal angiomyolipoma with minimal fat: differentiation from other neoplasms at double-echo chemical shift FLASH MR imaging. Radiology 2006;239:174-80.
4. Li H, Liang L, Li A, Hu Y, Hu D, Li Z, et al. Monoexponential, biexponential, and stretched exponential diffusion-weighted imaging models: Quantitative biomarkers for differentiating renal clear cell carcinoma and minimal fat angiomyolipoma. J Magn Reson Imaging 2017;46:240-7.
5. Wang H, Cheng L, Zhang X, Wang D, Guo A, Gao Y, et al. Renal cell carcinoma: diffusion-weighted MR imaging for subtype differentiation at 3.0 T. Radiology 2010;257:135-43.
6. Yu X, Lin M, Ouyang H, Zhou C, Zhang H. Application of ADC measurement in characterization of renal cell carcinomas with different pathological types and grades by 3.0T diffusion-weighted MRI. Eur J Radiol 2012;81:3061-6.

7. Tanaka H, Yoshida S, Fujii Y, Ishii C, Tanaka H, Koga F, et al. Diffusion-weighted magnetic resonance imaging in the differentiation of angiomyolipoma with minimal fat from clear cell renal cell carcinoma. Int J Urol 2011;18:727-30.
8. Hötker AM, Mazaheri Y, Wibmer A, Zheng J, Moskowitz CS, Tickoo SK, et al. Use of DWI in the Differentiation of Renal Cortical Tumors. AJR Am J Roentgenol 2016;206:100-5.
9. Li H, Li A, Zhu H, Hu Y, Li J, Xia L, et al. Whole-Tumor Quantitative Apparent Diffusion Coefficient Histogram and Texture Analysis to Differentiation of Minimal Fat Angiomyolipoma from Clear Cell Renal Cell Carcinoma. Acad Radiol 2019;26:632-9.
10. Chen LS, Zhu ZQ, Wang ZT, Li J, Liang LF, Jin JY, et al. Chemical shift magnetic resonance imaging for distinguishing minimal-fat renal angiomyolipoma from renal cell carcinoma: a meta-analysis. Eur Radiol 2018;28:1854-61.
11. Just N. Improving tumour heterogeneity MRI assessment with histograms. Br J Cancer 2014;111:2205-13.
12. Li XL, Shi LX, Du QC, Wang W, Shao LW, Wang YW. Magnetic resonance imaging features of minimal-fat angiomyolipoma and causes of preoperative misdiagnosis. World J Clin Cases 2020;8:2502-9.
13. Chen CL, Tang SH, Wu ST, Meng E, Tsao CW, Sun GH, et al. Calcified, minimally fat-contained angiomyolipoma clinically indistinguishable from a renal cell carcinoma. BMC Nephrol 2013;14:160.
14. Hindman N, Ngo L, Genega EM, Melamed J, Wei J, Braza JM, et al. Angiomyolipoma with minimal fat: can it be differentiated from clear cell renal cell carcinoma by using standard MR techniques? Radiology 2012;265:468-77.
15. Tordjman M, Mali R, Madelin G, Prabhu V, Kang SK. Diagnostic test accuracy of ADC values for identification of clear cell renal cell carcinoma: systematic review and meta-analysis. Eur Radiol 2020;30:4023-38.
16. Zhang Y, Chen J, Liu S, Shi H, Guan W, Ji C, et al. Assessment of histological differentiation in gastric cancers using whole-volume histogram analysis of apparent diffusion coefficient maps. J Magn Reson Imaging 2017;45:440-9.
17. Baek HJ, Kim HS, Kim N, Choi YJ, Kim YJ. Percent change of perfusion skewness and kurtosis: a potential imaging biomarker for early treatment response in patients with newly diagnosed glioblastomas. Radiology 2012;264:834-43.
18. Kierans AS, Rusinek H, Lee A, Shaikh MB, Triolo M, Huang WC, et al. Textural differences in apparent diffusion coefficient between low- and high-stage clear cell renal cell carcinoma. AJR Am J Roentgenol 2014;203:W637-44.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:263-268
DOI: 10.4274/BMJ.galenos.2023.2023.3-4

Research

Microendoscopic Discectomy for Lumbar Disc Herniations: A Series of 389 Cases

Lomber Disk Herniasyonlarında Mikroendoskopik Diskektomi Yöntemi: 389 Olgu Serisi

Bülent Bozyiğit[1], Bilal Abbasoğlu[2], Caner Ünlüer[2], Göktuğ Ülkü[2], Abdullah Emre Taçyıldız[3], Hüseyin Hayri Kertmen[2]

[1]Gözde Akademi Hospital, Clinic of Neurosurgery, Malatya, Türkiye
[2]Ankara Etlik City Hospital, Clinic of Neurosurgery, Ankara, Türkiye
[3]Turgut Özal University Faculty of Medicine, Department of Neurosurgery, Malatya, Türkiye

ABSTRACT

Objective: Lumbar disc herniation is one of the discogenic causes of lower back pain. Patients with severe nerve root compression or progressive neurologic deficit who do not respond to conventional treatments require surgical intervention. These surgical treatments include minimally invasive and traditional methods. In this study, we have presented the clinical data of patients who underwent microendoscopic discectomy (MED)-a minimally invasive method.

Methods: The surgical and clinical data of 389 adult patients who were operated through MED by a single surgeon between 2017 and 2022 were retrospectively evaluated. Parameters such as perop-postop visual analog scale (VAS), follow-up time, duration of hospitalization, and amount of intraoperative blood loss were examined.

Results: Of the 389 patients included in our study, 169 were female and 220 were male, and their mean age was 42.78 years. L4-L5 (n=205, 51.6%), L5-S1 (n=185, 46.8%), L3-L4 (n=4, 1%), and L2-L3 (n=2, 0%) were the most frequently operated levels, showing a sequentially decreasing frequency. Bilateral surgery was performed in two patients. Recurrence was observed in 11 patients (2.8%). Cerebrospinal fluid was detected in 2 (0.5%) patients. The mean pre- and post-op VAS scores were calculated as 7.45 and 1.14, with a significant difference of $p<0.001$. The mean blood loss during surgery was calculated as 9.6±5.8 mL, and the postoperative hospital stay was 17.2±8.5 hours.

Conclusion: MED was comparable to conventional methods in terms of symptom relief, recurrence rate, recovery time after surgery, and intraoperative blood loss.

Keywords: Lumbar disc herniation, microendoscopic discectomy, minimally invasive spinal surgery

ÖZ

Amaç: Lomber disk herniasyonu bel ağrısının diskojenik sebeplerinden biridir. Konvansiyonel tedavilere yanıt alınmayan, ciddi sinir kökü basısı bulguları veya ilerleyici nörolojik defisiti bulunan hastalara cerrahi müdahale gerekmektedir. Cerrahi tedavide, geleneksel yöntemlerin yanında minimal invaziv yöntemler de mevcuttur. Bu çalışmada, minimal invaziv yöntem olan mikroendoskopik diskektomi (MED) ile ameliyat edilmiş hastaların klinik verilerinin sunulması amaçlanmıştır.

Gereç ve Yöntem: 2017 ve 2022 yılları arasında tek cerrah tarafından, MED yöntemi ile ameliyat edilmiş 389 erişkin hastanın cerrahi ve klinik verileri retrospektif olarak değerlendirildi. Perop-postop vizüel analog skala (VAS), takip süresi, hastanede yatış süresi ve intraoperatif kan kaybı miktarı gibi parametreler detaylı bir şekilde incelendi.

Bulgular: Çalışmamıza dahil edilen 389 hastanın 169'u kadın 220'si erkek hastaydı ve hastaların yaş ortalaması 42,78 idi. L4-L5 (n=205, %51,6), L5-S1 (n=185, %46,8), L3-L4 (n=4, %1) ve L2-L3 (n=2, %0,5), azalan sıklıkla, en sık ameliyat edilen seviyelerdi. İki hastada çift taraflı ameliyat yapıldı. On bir hastada nüks izlendi (%2,8). İki (%0,5) hastada BOS (beyin omurilik sıvısı) gelişi oldu. Ortalama pre-op ve post-op VAS skoru 7,45 ve 1,14 olarak hesaplandı ve aradaki fark anlamlı bulundu ($p<0,001$). Cerrahi sırasında kan kaybı ortalama 9,6±5,8 mL olarak hesaplandı. Ameliyat sonrası hastanede kalma süresi 17,2±8,5 saatti.

Address for Correspondence: Bülent Bozyiğit, Gözde Akademi Hospital, Clinic of Neurosurgery, Malatya, Türkiye
E-mail: bulentbzt@yahoo.com ORCID ID: orcid.org/0000-0001-5038-2260

Cite as: Bozyiğit B, Abbasoğlu B, Ünlüer C, Ülkü G, Taçyıldız AE, Kertmen HH. Microendoscopic Discectomy for Lumbar Disc Herniations: A Series of 389 Cases. Med J Bakirkoy 2023;19:263-268

Received: 27.03.2023
Accepted: 04.07.2023

Sonuç: MED semptomların giderilmesi, nüks oranı, cerrahi sonrası iyileşme süresi, cerrahi sırasındaki kan kaybı açısından konvansiyonel yöntemlerle karşılaştırılabilecek derecede başarılı bulunmuştur.

Anahtar Kelimeler: Lomber disk herniasyonu, mikroendoskopik diskektomi, minimal invaziv spinal cerrahi

INTRODUCTION

Approximately 60-80% people complain of lower back pain at least once in their lives (1). Lumbar disc herniation (LDH) is one of the discogenic causes of lower back pain. Patients with severe nerve root compression or progressive neurologic deficit who do not respond to conventional treatments for 6 weeks may require surgical intervention. Presently, LDHs with surgical indications are treated via surgical approaches such as open discectomy (OD) and minimally invasive methods such as microdiscectomy (MD), microendoscopic discectomy (MED), and percutaneous endoscopic discectomy.

OD for lumbar disc hernias was first reported in 1934 by Mixter and Barr (2). In this surgical technique, paravertebral muscle stripping and total laminectomy or hemilaminectomy are performed after the standard skin incision. Next, when the microscope begins to enter the surgical field, it was also used by surgeons in lumbar discectomy, and the lumbar discectomy procedure with the microsurgery technique was first documented in 1977 by Yasargil (3) and Caspar (4). Subsequently, this technique gained popularity and, until recently, it was the most preferred surgical method for lumbar discectomy.

Technological advances and the search for a more minimally invasive approach led to the use of an endoscope in lumbar discectomy, and the first step in this direction was taken by Foley and Smith (5). In this minimally invasive technique, termed MED, nerve root decompression is performed using an endoscope. This MED system was modified as the Microscopic Endoscopic Tubular Retraction System [METRx (Medtronic Sofamor Inc., Memphis, TN, USA) in 1999] and customized for use with both a microscope and an endoscope (6).

Although neurological improvement is achieved with OD, complications are frequently observed in the postoperative period due to damage to the paraspinal muscles, connective tissues, and ligamentum flavum during surgery, with prolonged recovery times. As an alternative and less invasive surgical approach, MED is frequently preferred as the surgical approach of choice. As it is less invasive, the damage to the paraspinal muscles is less via this approach. However, some studies have demonstrated that clinical improvement [reduction in the visual analog scale (VAS) scores] was comparable to that with other methods. Some studies argue that MED is unsuccessful compared to other minimally invasive methods (7). Therefore, much more work is needed to obtain more accurate data when comparing MED with the other methods. Accordingly, in our study, we have presented the clinical results of patients who were operated on by MED.

METHODS

In this study, 389 adult patients who were operated on via MED by a single surgeon at a single center between 2017 and 2022 in our clinic were included. The surgical and clinical data of the patients were retrospectively evaluated. Parameters such as preop-postop VAS, follow-up time, duration of hospitalization, and amount of intraoperative blood loss were examined. Patients with spondylolisthesis-associated disc herniation, spondylodiscitis, diffuse lumbar stenosis, irregular postoperative follow-ups, and spondylodiscitis for whom sufficient arguments could not be reached were excluded from the study despite being operated on with the MED method.

This study was approved by the Malatya Turgut Özal University, Non-Invasive Clinical Research Ethics Committee (no: 2022/216, date: 13.12.2022). Written informed consent was obtained from the patient.

Statistical Analysis

Statistical analyses were performed using the SPSS program. Continuous variables were expressed as mean and categorical variables as percentages. The chi-square test was performed for the difference between categorical variables and the t-test was performed for the difference between continuous variables. The paired sample test was performed to evaluate the variation in continuously calculated value in the same sample over time.

Surgical Technique

The patients were placed in the prone position on a radiolucent surgical table under spinal epidural anesthesia. Cefazolin or ceftriaxone was given as a prophylactic antibiotic. The surgical table was bent to appropriately open the lumbar spine-the interlaminar space. The sides are supported with a pillow to avoid abdominal compression. The following distance determination with a 20-gage spinal needle under C-arm fluoroscopy (Figure 1A), the incision line was determined. After cleaning the surgical field and

appropriate sterile draping, a 1.5-2 cm skin incision was made 1-2 cm lateral to the midline entering from the symptomatic side, and the incision was deepened to include the lumbar fascia. After the incision, a spinal endoscopy system EasyGo (Karl Storz, Tuttlingen, Germany) was placed. This system consisted of a high-resolution camera, a 30° wide-view telescope with adjustable size, and several series of tubular dilators and retractors. It was advanced from the smallest muscles (5.2-mm diameter) to the lamina by a twisting motion (Figure 1B). The sweeping action of the dilator also helped in subperiosteal muscle separation. Examination with lateral fluoroscopy ensured that the dilator position was at the correct level. Larger dilators were placed sequentially until the appropriate dilator was deployed (Figure 1C). At each stage, the bony structure was felt with a dilator, thus avoiding inadvertent penetration of the interlaminar space. The tubular retractor (15, 19 or 23 mm) was placed after the dilators and connected to the flexible arm fixed to the operating table. Finally, the endoscope was carefully inserted and connected to the tubular retractor using the corresponding insert (Figure 1C). The video monitor was set in the front of the operating table facing the surgical team. The was examined again with lateral fluoroscopy before securing the endoscope system to the tubular retractor (Figure 1D). The endoscope camera system was set at 6 o'clock relative to the surgeon on a fixed tubular retractor to ensure that the orientation on the monitor matched the actual anatomical orientation. Hemipartial laminectomy was then performed using a Kerrison rongeur and high-speed tour. Using a dissector or curette, the ligamentum flavum was opened and separated from the superior lamina. The fragments were then collected with a Kerrison rongeur. After the tecal sac dura and nerve root were visualized, they were dissected with a Penfield dissector or blunt nerve trunk (Figure 2A).

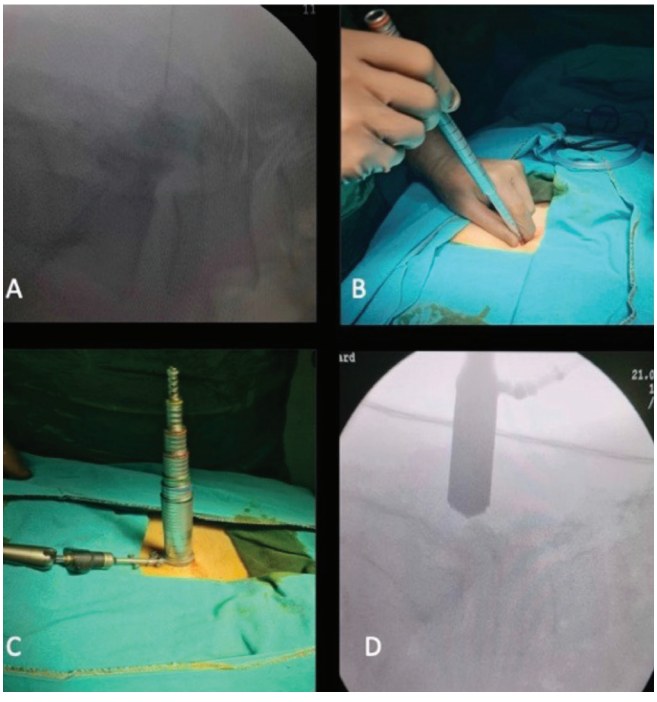

Figure 1. Placement of the MED system
MED: Microendoscopic discectomy

The nerve root is excised with the help of a retractor to expose the disc. In case of bleeding from epidural veins, it can be coagulated with bipolar forceps. After the disc fragment is freed, it is grasped with forceps and removed (Figure 2B-D). If the fragment is under the capsule, the capsule needs to be cut. For this, special hooked scissors can be used and then the herniated disc content can be removed. After the bleeding was controlled, the surgical cavity was washed with plenty of saline. The tubular system was removed and the operation was terminated by closing the layers in the anatomical plane. In the early postoperative period, the patient was documented by MRI and comparing the pre- and postoperative images (Figure 3).

RESULTS

A total of 389 patients who were operated on via the microendoxopic approach were included in the study. There were 169 female and 220 male patients (F:M=0.76). The mean age at the time of surgery was 42.78 years (standard deviation =11.56). A total of 395 levels were operated on in

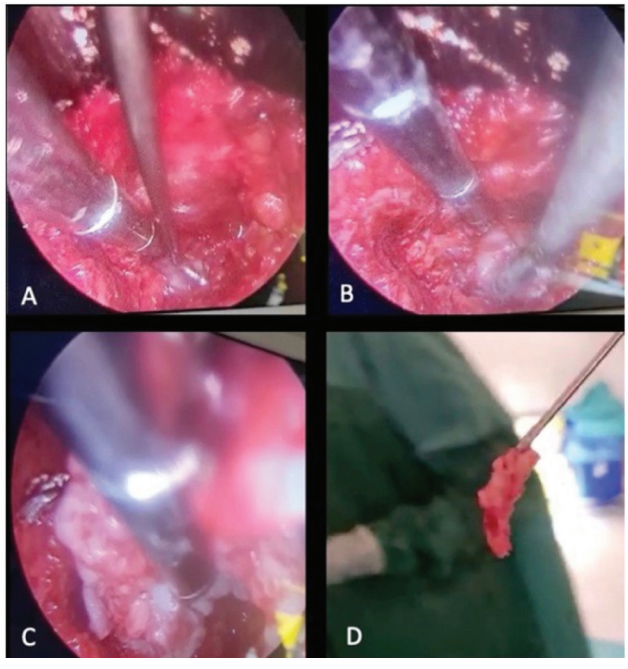

Figure 2. Removal of herniated disc contents

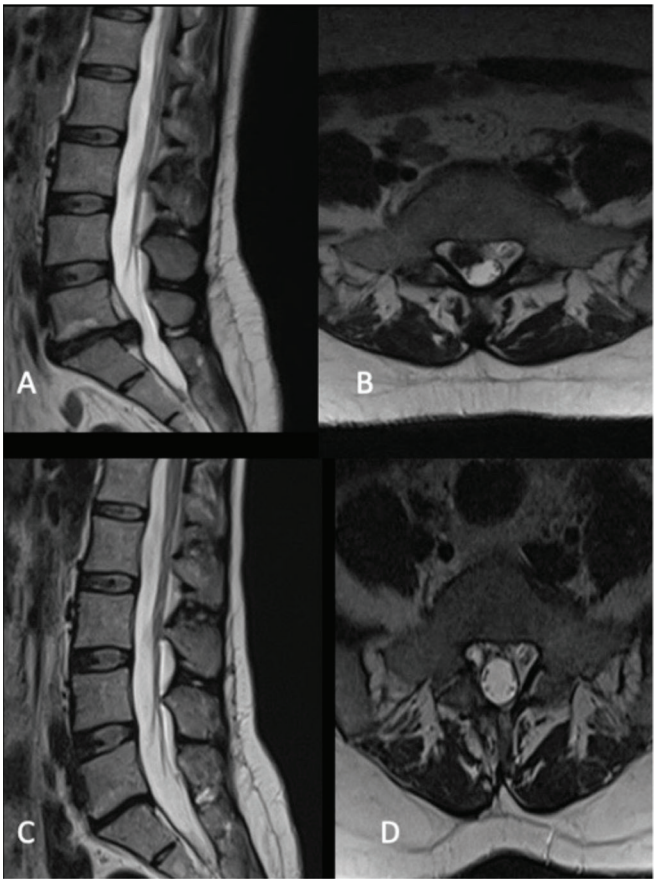

Figure 3. Pre-op and post-op T2 sequence magnetic resonance images

389 patients (two levels were operated on 6 patients). L4-L5 (n=205, 51.6%), L5-S1 (n=185, 46.8%), L3-L4 (n=4, 1%), and L2-L3 (n=2, 0%) were the most frequently operated levels, with a decreasing frequency (Table 1). Bilateral surgery was performed on two patients. The remaining patients underwent unilateral surgery.

Recurrence was recorded in 11 patients (2.8%). Two of these relapses were followed in the first month and the remaining within the first year. Seven of these patients underwent repeat MED and the other four underwent OD.

CSF was detected in only two (0.5%) patients. There were no complications such as nerve root damage and neurological deficit in any patient.

VAS was recorded in the pre- and postoperative periods for clinical follow-up. The mean pre- and post-op VAS scores were calculated as 7.45 and 1.14, and the difference was significant ($p<0.001$). The mean time to postoperative VAS score recording was 8.41 months after surgery. Only two patients required postoperative scar revision (0.5%).

The mean amount of blood lost during the operation was calculated as 9.6±5.8 mL. The postoperative hospital stay was 17.2±8.5 hours (h).

Table 1. Data of patients who underwent surgery with the MED method

Particular	Value
Gender	
Woman	169 (43.4%)
Men	220 (56.6%)
Age (year ± SD)	42.8±11.6
Level (n, %)	
L1-L2	0 (0%)
L2-L3	2 (0.5%)
L3-L4	3 (0.8%)
L4-L5	199 (51.2%)
L5-S1	185 (47.6%)
Pre-op VAS	7.4±0.7
Post-op VAS	1±0.4
Amount of bleeding (cc ± SD)	10±5.8
Dural tail	2 (0.5%)
Follow-up time (month ± SD)	8±2.8
Hospital stay time (hour ± SD)	17±8.5
Recurrence	11 (3%)
Infection	0 (0%)

MED: Microendoscopic discectomy, SD: Standard deviation, VAS: Visual analog scale

DISCUSSION

In the management of patients with LDH with surgical indications, the choice of surgical method is determined based on the surgeon's experience, available technical capacity, and patient-related factors. Endoscopic approaches allow for smaller incisions and less tissue trauma compared with standard open MD. Because the MED procedure causes significantly less iatrogenic damage to the paraspinal musculature, it can provide additional long-term benefits. OD was once considered the "gold standard" treatment for LDH (8). However, the tendency toward minimally invasive methods is gradually increasing because it disrupts the posterior structure of the spine and causes segmental instability and long-term problems.

The MED technique, which emerged as an alternative to OD introduced by Smith and Foley, has been used successfully for treating LDH since 1997 (5,9). The optimal indication for MED has been defined as unilevel radiculopathy secondary to LDH (5). The use of MED is not recommended in patients with segmental instability and lower back pain-related herniation, lumbar stenosis and herniation, or previous

lumbar surgery (10). This factor does not indicate that surgeries cannot be performed using the MED method. It needs to be emphasized that these surgeries are very difficult for a beginner-level surgeon and may increase the complication rate if not performed correctly; thus, advanced experience in the MED method is required.

The success rate for MED has been described as 90% in the literature, and the recurrence rate has been reported as approximately 5% (11). In this case series, recurrence was observed in only 11 of the 389 patients, with a recurrence rate of approximately 3%.

In a randomized comparative study by Teli et al. (7), the recurrence rate was 11.4%, and the rate of dura and root damage, motor deficit, and spondylodiscitis was higher in patients operated on by the MED method when compared to MD and OD. When the study was examined, we noted that the surgical experience of the doctors adopting the MD and OD methods was twice that of a surgeon adopting the MED method, and the number of patients was insufficient. Such factors make us reluctant to reach a definite conclusion and make any comparisons. In our study, the recurrence rate was 3% and dural damage was 0.5%, and when combined with the absence of complications such as root injury, spondylodiscitis, and motor deficits, our opinion seems justified.

In the study of Wu et al. (6), in which they published the data of 873 patients who underwent surgery with the MED method, preop and postoperative VAS scores were 7.8 and 2.3, respectively. The mean blood loss and hospital stay duration was 44 cc and 4.8 days, respectively. In our study, preop and postoperative VAS scores were calculated to be 7.45 and 1.14; these findings were similar to those of Wu et al. The mean amount of blood lost during the operation was 9.6±5.8 mL, while the postoperative hospital stay was 17.2±8.5 h. In addition to the complication rates, the low blood loss that occurred during the operation and the shorter length of stay in the hospital acted as important indicators of comfort for the patients.

One of the most important reasons for shorter hospital stays in MED patients is the minimal level of paraspinal muscle damage compared with OD (12). Other factors that may be associated with rapid healing are limited traumatic nerve root dissection, less bone removal, and shorter skin incision (13). According to Cheng et al. (14), the amount of intraoperative damage is less in MED patients than in OD patients.

In our study, only two patients needed scar revision in the postoperative period. In addition, no wound or infective complication was encountered during the postoperative period. Li et al. (15) reported that although the complication rate in MED patients was numerically higher than that in OD, this difference was not statistically significant.

Masuda et al. (16) evaluated 3961 patients who were operated on with the MED, MD, and OD methods. Although it was stated that this rate was higher than MD and OD, it was not significant when the age, gender, and comorbidities of the patients were considered.

Several studies are comparing the MED method with percutaneous endoscopic lumbar discectomy (PLED). In a study by Xu et al. (17), in which these studies were meta-analyzed, 9 studies, 516 in the MED group and 468 in the PLED group, were evaluated.

Because of meta-analysis, no difference was detected between the two groups in the preop-postop VAS scores for complications, recurrence, reoperation, and leg pain. It was determined that the PLED method gave better results than the MED method in terms of the evaluation of VAS for lower back pain. This meta-analysis revealed that the results of the MED method compete with those of other minimally invasive methods.

In conclusion, according to our study, MED emerged as a preferred method with a low complication rate. However, the MED technique involves a learning curve that must be carefully overcome. The two-dimensional endoscopic view and hand-eye coordination can also confusing compared with open surgery. Other variables affecting the learning curve include familiarity with instruments, three-dimensional understanding, and the command of anatomical structures. To master the MED procedure, the surgeon must willingly invest a significant amount of time and effort in relevant education and training. For a surgeon who has completed the learning curve, maintaining and publishing records of surgeries performed with the MED technique is as important as the surgery itself to allow for healthier comparisons in the future.

CONCLUSION

MED is a less invasive surgical method developed as an alternative to the related conventional methods. Damage to the paraspinal muscles, ligamentum flavum, and other soft tissues is less common in surgeries performed using MED. Moreover, the recovery period after this surgery was shorter. In our study, clinical and surgical data of 389 patients who underwent discectomy with MED are presented. MED was found to be comparable to conventional methods in terms of symptom relief, recurrence rate, recovery time after surgery, and intraoperative blood loss.

ETHICS

Ethics Committee Approval: This study was approved by the Malatya Turgut Özal University, Non-Invasive Clinical Research Ethics Committee (no: 2022/216, date: 13.12.2022).

Informed Consent: Written informed consent was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: B.B., Concept: B.B., B.A., A.E.T., H.H.K., Design: B.A., G.Ü., H.H.K., Data Collection or Processing: B.B., C.Ü., Analysis or Interpretation: B.B., B.A., G.Ü., A.E.T., Literature Search: B.A., C.Ü., Writing: B.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Chang X, Chen B, Li HY, Han XB, Zhou Y, Li CQ. The safety and efficacy of minimally invasive discectomy: a meta-analysis of prospective randomised controlled trials. Int Orthop 2014;38:1225-34.
2. Mixter WJ, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. New England Journal of Medicine 1934;211:210-5.
3. Yasargil MG. Microsurgical Operation of Herniated Lumbar Disc. Lumbar Disc Adult Hydrocephalus. Advances in Neurosurgery. 4. Berlin, Heidelberg: Springer, Berlin, Heidelberg; 1977. p. 81-2.
4. Caspar W. A New Surgical Procedure for Lumbar Disc Herniation Causing Less Tissue Damage Through a Microsurgical Approach. Lumbar Disc Adult Hydrocephalus. 4. Berlin, Heidelberg: Springer, Berlin, Heidelberg; 1977. p. 74-80.
5. Foley KT. Microendoscopic discectomy. Techniques in neurosurgery 1997;3:301-7.
6. Wu X, Zhuang S, Mao Z, Chen H. Microendoscopic discectomy for lumbar disc herniation: surgical technique and outcome in 873 consecutive cases. Spine (Phila Pa 1976) 2006;31:2689-94.
7. Teli M, Lovi A, Brayda-Bruno M, Zagra A, Corriero A, Giudici F, et al. Higher risk of dural tears and recurrent herniation with lumbar micro-endoscopic discectomy. Eur Spine J 2010;19:443-50.
8. Apostolides PJ, Jacobowitz R, Sonntag VK. Lumbar discectomy microdiscectomy: "the gold standard". Clin Neurosurg 1996;43:228-38.
9. Perez-Cruet MJ, Foley KT, Isaacs RE, Rice-Wyllie L, Wellington R, Smith MM, et al. Microendoscopic lumbar discectomy: technical note. Neurosurgery 2002;51(5 Suppl):S129-36.
10. Muramatsu K, Hachiya Y, Morita C. Postoperative magnetic resonance imaging of lumbar disc herniation: comparison of microendoscopic discectomy and Love's method. Spine (Phila Pa 1976) 2001;26:1599-605.
11. Ruetten S, Komp M, Merk H, Godolias G. Full-endoscopic interlaminar and transforaminal lumbar discectomy versus conventional microsurgical technique: a prospective, randomized, controlled study. Spine (Phila Pa 1976) 2008;33:931-9.
12. Patil A, Chugh A, Gotecha S, Kotecha M, Punia P, Ashok A, et al. Microendoscopic discectomy for lumbar disc herniations. J Craniovertebr Junction Spine 2018;9:156-62.
13. Garg B, Nagraja UB, Jayaswal A. Microendoscopic versus open discectomy for lumbar disc herniation: a prospective randomised study. J Orthop Surg (Hong Kong) 2011;19:30-4.
14. Cheng J, Wang H, Zheng W, Li C, Wang J, Zhang Z, et al. Reoperation after lumbar disc surgery in two hundred and seven patients. Int Orthop 2013;37:1511-7.
15. Li WS, Yan Q, Cong L. Comparison of Endoscopic Discectomy Versus Non-Endoscopic Discectomy for Symptomatic Lumbar Disc Herniation: A Systematic Review and Meta-Analysis. Global Spine J 2022;12:1012-26.
16. Masuda S, Fukasawa T, Takeuchi M, Fujibayashi S, Otsuki B, Murata K, et al. Reoperation Rates of Microendoscopic Discectomy Compared With Conventional Open Lumbar Discectomy: A Large-database Study. Clin Orthop Relat Res 2022;481:145-54.
17. Xu J, Li Y, Wang B, Lv G, Li L, Dai Y, et al. Minimum 2-Year Efficacy of Percutaneous Endoscopic Lumbar Discectomy versus Microendoscopic Discectomy: A Meta-Analysis. World Neurosurg 2020;138:19-26.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:269-275
DOI: 10.4274/BMJ.galenos.2023.2023.3-20

Research

Biologic Therapies in Juvenile Idiopathic Arthritis

Jüvenil İdiyopatik Artritte Biyolojik Tedaviler

Ayşe Tanatar, Nuray Aktay Ayaz

İstanbul University, İstanbul Faculty of Medicine, Department of Pediatric Rheumatology, İstanbul, Türkiye

ABSTRACT

Objective: To investigate the single-center experience of the efficacy and safety profile of biologic therapies in patients with juvenile idiopathic arthritis (JIA) and identify risk factors associated with adverse events (AEs).

Methods: The medical charts of children with JIA diagnosed between January 2010 and December 2021 were reviewed retrospectively, and patients treated with biological agents were included in the study. Demographic data, clinical features, laboratory results, treatments used, and AEs during the treatment period were collected.

Results: From the total JIA cohort (n=814), 237 patients who received biologic therapy for at least 3 months were enrolled in the study. The most frequent subtype was persistent oligoarticular JIA (45.1%) and the most frequently used biologic drug was etanercept (n=118), followed by adalimumab (n=64), tocilizumab (n=31), anti-interleukin-1 (anti-IL-1) agents (n=12; 7 anakinra and 5 canakinumab), infliximab (n=6), abatacept (n=3), secukinumab (n=2) and tofacitinib (n=1). One hundred sixty-four (69.2%) patients received disease-modifying antirheumatic drugs (DMARDs) concomitantly, 10.5% received DMARDs plus corticosteroids and 2.1% received only corticosteroids. The median [interquartile range (IQR)] age and median age at initiation of the biologics were 14.4 (10.7-18) years and 10.9 (6.6-14.5) years, respectively. The median (IQR) follow-up period was 3.9 (2-6.3) years. On biologic therapy, the median (IQR) JADAS-71 decreased from 13 (11-19) at baseline to 0 (0-2) after median 22 (10-40) months of treatment (p<0.001). The most frequent AE was local injection site reactions with biologics administered subcutaneously (n=8), followed by upper respiratory tract infections (n=4) and diffuse erythematous skin rashes (n=4). Serious AEs were observed in 11 (4.6%) patients. To compare the frequency of AEs, patients were divided into three groups according to the biologics administered, as follows: Group 1: Tumor necrosis factor inhibitors, group 2: anti-IL-1 agents, group 3: anti-IL-6 agent. The frequency of AEs was significantly higher in JIA patients on anti-IL-1 therapy than in the other two groups (58.3% vs. 29% and 8.5%, p<0.001).

Conclusion: Biological agents are used with increasing frequency in children with JIA, and their off-label use is quite common. Although these agents are considerably effective and quite safe, AEs should not be underestimated. While planning the management of patients with refractory JIA, careful interpretation of benefit-risk balance for every individual patient seems to be reasonable and required.

Keywords: Adverse events, biologic therapy, juvenile idiopathic arthritis

ÖZ

Amaç: Jüvenil idiyopatik artrit (JİA) hastalarında biyolojik tedavilerin etkinlik ve güvenlik profiline ilişkin tek merkez deneyimini araştırmak ve olumsuz olaylarla (AE'ler) ilişkili risk faktörlerini belirlemektir.

Gereç ve Yöntem: Ocak 2010-Aralık 2021 tarihlerinde JİA tanısı alan çocukların tıbbi dosyaları retrospektif olarak incelendi ve biyolojik ajanlarla tedavi edilen hastalar çalışmaya dahil edildi. Tedavi süresince demografik veriler, klinik özellikler, laboratuvar sonuçları, kullanılan tedaviler ve AE'ler toplandı.

Bulgular: Toplam JİA kohortundan (n=814) en az 3 ay biyolojik tedavi almış 237 hasta çalışmaya alındı. En sık görülen JİA alt tipi persistan oligoartiküler JİA'ydı (%45,1) ve en sık kullanılan biyolojik ilaç etanerseptti (n=118), bunu sırasıyla adalimumab (n=64), tosilizumab (n=31), anti-interlökin-1 (anti-IL-1) ajanlar (n=12; 7 anakinra ve 5 kanakinumab), infliksimab (n=6), abatasept (n=3), sekukinumab (n=2) ve tofasitinib (n=1) izledi. 164 (%69,2) hasta eş zamanlı olarak hastalık modifiye edici antiromatizmal ilaç (DMARD), %10,5'i DMARD ve kortikosteroid ve %2,1'i sadece kortikosteroid almıştır. Hastaların medyan [çeyrekler açıklığı (IQR)] yaşı 14,4 (10,7-18) yıl ve biyolojik ilaçların başlangıcındaki medyan yaşları 10,9 (6,6-14,5) yıldı. Medyan (IQR) takip süresi 3,9 (2-6,3) yıldı. Medyan 22 (10-40) aylık biyolojik tedavi ile başlangıçtaki medyan (IQR) JADAS-71 13'ten (11-19) tedaviden sonra 0'a (0-2) düştü (p<0,001). En sık görülen AE, subkütan uygulanan biyolojiklerle lokal enjeksiyon yeri reaksiyonlarıydı (n=8), bunu üst solunum yolu enfeksiyonları (n=4) ve yaygın eritematöz deri döküntüleri (n=4) izledi. On bir (%4,6) hastada ciddi

Address for Correspondence: Nuray Aktay Ayaz, İstanbul University, İstanbul Faculty of Medicine, Department of Pediatric Rheumatology, İstanbul, Türkiye
Phone: +90 532 621 22 14 E-mail: nurayaktay@gmail.com ORCID ID: orcid.org/0000-0003-3594-7387

Cite as: Tanatar A, Aktay Ayaz N. Biologic Therapies in Juvenile Idiopathic Arthritis. Med J Bakirkoy 2023;19:269-275

Received: 26.04.2023
Accepted: 24.07.2023

AE gözlendi. AE'lerin sıklığını karşılaştırmak için, hastalar uygulanan biyolojiklere göre aşağıdaki gibi üç gruba ayrıldı: Grup 1: Tümör nekroz faktör inhibitörleri, grup 2: anti-IL-1 ajanlar, grup 3: anti-IL-6 ajan. AE sıklığı, anti-IL-1 tedavisi alan JİA hastalarında diğer iki gruba göre anlamlı olarak daha yüksekti (%58,3'e karşı %29 ve %8,5, p<0,001).

Sonuç: Biyolojik ajanlar JİA'lı çocuklarda artan sıklıkta kullanılmaktadır ve endikasyon dışı kullanımları da oldukça yaygındır. Bu ajanlar oldukça etkili ve güvenli olmalarına rağmen, yan etkileri hafife alınmamalıdır. Dirençli JİA hastalarının yönetimini planlarken, her bir hasta için fayda-risk dengesinin dikkatli bir şekilde yorumlanması makul ve gerekli görünmektedir.

Anahtar Kelimeler: Advers olaylar, biyolojik tedavi, jüvenil idiyopatik artrit

INTRODUCTION

The most prevalent pediatric rheumatic disease is juvenile idiopathic arthritis (JIA), which is classified into seven subtypes by the International League of Associations for Rheumatology: oligoarticular (oJIA), rheumatoid factor (RF) negative and positive polyarticular (pJIA), systemic (sJIA), psoriatic arthritis (PsA), enthesitis-related (ERA), and undifferentiated arthritis (1).

Non-steroidal anti-inflammatory drugs, corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) are still the mainstay of JIA treatment. However, biologic drugs are increasingly used when remission cannot be achieved with these main treatments or as initial therapy in patients with aggressive diseases.

During the past 20 years of the biologic era, restoring synovitis and tissue damage, preventing extraarticular complications, and providing low disease activity became achievable goals in JIA. However, the increased risk of infections and the potential threat of malignancy are critical issues that should be considered while making a decision about the biologic therapy (2).

This study analyzed the efficacy and safety profile of biologic therapies in JIA patients followed by a tertiary reference hospital.

METHODS

Patients

The medical charts of 237 patients treated with biologic agents out of 814 JIA patients who were diagnosed with JIA and followed up regularly every 1-3-month intervals in the Pediatric Rheumatology Unit of İstanbul Faculty of Medicine, İstanbul University, Türkiye between January 2010 and December 2021 were reviewed retrospectively. The patients who received biologic therapy for at least 3 months and at least 6 months of follow-up were included in the study. Demographic characteristics, clinical features, laboratory tests and treatment modalities, and adverse events (AEs) during the treatment period were retrospectively collected.

The juvenile arthritis disease activity score-71 (JADAS-71) was calculated to assess disease activity and was calculated as follows: physician visual analog scale (VAS) + patient VAS + active joint count + erythrocyte sedimentation rate (ESR)-20/10 (3). Response to treatment was defined according to JADAS-71 (4). The criteria described by Wallace et al. (5) was used for the definition of inactive disease as no active arthritis or uveitis; a physician's global assessment indicating no disease activity; no fever, rash, serositis, splenomegaly, or lymphadenopathy; and no elevated ESR or C-reactive protein level attributable to JIA.

TNFi (etanercept, adalimumab, and infliximab), interleukin (IL)-1 antagonist (anakinra and canakinumab), anti-IL-6 agent (tocilizumab) and cytotoxic T-lymphocyte-associated protein 4 agonist (abatacept), IL-17A receptor antagonist (secukinumab) and janus-kinase inhibitor (tofacitinib) were the biologics used by the patients.

AEs and serious adverse events (SAEs) were recorded from the patients' medical charts. SAEs were considered AEs that resulted in death, life-threatening, hospitalization, malignancy, or permanent or significant disability/incapacity (6).

This study was approved by the Institutional Review Board of İstanbul University, İstanbul Faculty of Medicine (decision no: 07, date: 08.04.2022), and informed consent was obtained from all patients/parents.

Statistical Analysis

Statistical analysis was carried out using SPSS software version 28.0. Descriptive statistics are presented as proportions for categorical variables. Chi-square test or Fisher's Exact test was used to compare categorical variables, whichever was appropriate. The normality of continuous data was assessed using the Shapiro-Wilk tests. Continuous data were expressed as median and interquartile ranges (IQR) when not normally distributed and mean ± standard deviation when normally distributed. Independent samples t-test or Mann-Whitney U test were used to compare the continuous variables. All statistical analyzes were carried out at a 5% significance level and an overall p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

Of 237 patients, 122 (51.5%) were male. The most common subtype was persistent oJIA (45.1%). With a median 46.4 (IQR 24-76) months follow-up, the duration of biologic drug usage was median 22 months (IQR 10-40). Demographic features, the distribution of the JIA subgroups, and the biologic therapies used for the patients are shown in Table 1.

A total of 22 (9.3%) patients had uveitis, and 8 of them were diagnosed with uveitis at baseline, while 14 patients had uveitis during follow-up. Six of the 14 patients were on etanercept therapy, and the remaining 8 patients were on methotrexate therapy at the time of diagnosis of uveitis. Of the 22 patients with uveitis, 18 patients had persistent oJIA, 3 patients had RF (-) pJIA, one patient had PsA.

Antinuclear antibody (ANA) test positivity for the whole cohort was 32.5% (n=77) and 17 (70.8%) of them experienced uveitis (p<0.001).

The most frequently used biologic drug was etanercept 49.8% (n=118), followed by adalimumab 27% (n=64), and tocilizumab 13% (n=31); respectively. One hundred sixty-four (69.2%) patients received DMARDs, 10.5% received DMARDs plus corticosteroids, and 2.1% received corticosteroids concomitantly.

Biologic agents were switched one time in 41 (80.4%) patients, 2 times in 3 (5.9%) patients, and 3 times in 7 (13.7%) patients, in 51 (21.5%) patients.

On biologic therapy, the median (IQR) JADAS-71 decreased from 13 (11-19) at baseline to 0 (0-2) after median 22 (10-40) months of treatment (p<0.001). At the last visit, 118 (49.8%) patients were still receiving biologic therapy. Biologics were discontinued in 36 (15.2%) patients due to inactive disease during follow-up. Nine patients (25%) experienced disease flare after 10 (2-46) months of biologic (b)DMARDs cessation. The remaining 27 patients maintained remission to the last visit. The median follow-up period after biologic cessation was 1.2 (0.5-1.8) years.

When the patients were evaluated for AEs; it was seen that 27 (11.4%) patients experienced at least one AE. The most common AE was local injection site reactions (n=8) with biologics administered subcutaneously, followed by upper respiratory tract infections (n=4) and diffuse erythematous skin rashes (n=4) (Table 2).

SAEs were observed in 11 (4.6%) patients (Table 2). Three of these patients had sJIA using anakinra. Anakinra was discontinued in one patient because of the development of diffuse hypersensitivity reaction and angioedema after the first dose. Concomitant cytomegalovirus (CMV)

Table 1. The demographic characteristics, the distribution of disease subgroups, and biologic therapies used for juvenile idiopathic arthritis patients

Parameters	Numerical values
Demographic characteristics	
Gender (female/male), n (%)	115/122 (48.5/51.5)
Age, years (median, IQR)	14.4 (10.7-18)
Age at disease onset, years (median, IQR)	8.5 (3.2-11.9)
Age at diagnosis, years (median, IQR)	9 (4.3-12.6)
The disease duration, years (median, IQR)	4.6 (2.5-7)
The delay in diagnosis, months (median, IQR)	2.4 (1-8.6)
Follow-up period, years (median, IQR)	3.9 (2-6.3)
Age at biologic onset, years (median, IQR)	10.9 (6.6-14.5)
The disease duration at initiation of biologic therapy, months (median, IQR)	21.2 (8-37)
The duration of biologic therapy usage, months (median, IQR)	22 (10-40)
Biologic switch, n (%)	51 (21.5)
One time switch, n (%)	41 (80.4)
Two times switch, n (%)	3 (5.9)
≥ 3 times switch, n (%)	7 (13.7)
JIA subtypes	
Oligoarticular JIA, n (%)	115 (48.5)
Persistent, n (%)	107 (45.1)
Extended, n (%)	8 (3.4)
RF-negative polyarticular JIA, n (%)	35 (14.8)
Enthesitis-related arthritis JIA, n (%)	35 (14.8)
Systemic-onset JIA, n (%)	28 (11.8)
Psoriatic arthritis, n (%)	12 (5.1)
RF-positive polyarticular JIA, n (%)	10 (4.2)
Undifferentiated, n (%)	2 (0.8)
Biologic treatments	
Etanercept, n (%)	118 (49.8)
Adalimumab, n (%)	64 (27)
Tocilizumab, n (%)	31 (13)
Anakinra, n (%)	7 (3)
Infliximab, n (%)	6 (2.6)
Canakinumab, n (%)	5 (2.1)
Abatacept, n (%)	3 (1.3)
Secukinumab, n (%)	2 (0.8)
Tofacitinib, n (%)	1 (0.4)

Table 1. Continued

Concomitant therapy with biologic treatments	
DMARDs, n (%)	164 (69.2)
Methotrexate, n (%)	146 (61.6)
Sulphasalazine, n (%)	19 (8)
Leflunamide, n (%)	16 (6.8)
Ciclosporin, n (%)	8 (3.4)
DMARDs and corticosteroids, n (%)	25 (10.5)
Corticosteroids, n (%)	5 (2.1)

DMARDs: Disease-modifying antirheumatic drugs, JIA: Juvenile idiopathic arthritis, RF: Rheumatoid factor, IQR: Interquartile range

infection was detected in another patient who developed a diffuse hypersensitivity reaction at the second dose. The third patient presented with moderate to severe hepatic failure after the 12th dose of anakinra and recovered spontaneously after discontinuation of treatment. A patient using tocilizumab presented with convulsions after the 50th dose and neurological evaluation was consistent with posterior reversible encephalopathy syndrome (PRES) and the treatment was discontinued. No other pathology was found in the etiology. Pneumonia (one patient under etanercept and one patient under tocilizumab treatment) and presptal cellulitis (under etanercept treatment) requiring hospitalization developed in 3 patients. Two patients developed pulmonary tuberculosis under adalimumab treatment, and they both had Bacillus Calmette-Guérin vaccine before treatment.

For comparison of the frequency of AEs, patients were classified into three groups according to the administered biologics as follows (Table 2) (four patients using secukinumab, abatacept and tofacitinib were excluded due to the small number of patients):

- Group 1: TNFi (etanercept, adalimumab, and infliximab),
- Group 2: anti-IL-1 agents (anakinra and canakinumab),
- Group 3: anti-IL-6 agent (tocilizumab).

The frequency of AEs was significantly higher in JIA patients on anti-IL-1 therapy than in the other two groups (58.3% vs. 29% and 8.5%, p<0.001). However, most of them [3 of 7 AEs (42.9%)] were injection site reactions.

Although not statistically significant, children with sJIA (35.7%) had the highest risk of AEs, followed by PsA (16.7%), extended oJIA (12.5%), RF (+) pJIA (10%), ERA, RF (-) pJIA (8.6%), and persistent oJIA (5.6%).

Table 2. Comparison of the frequency of adverse events and serious adverse events between children with juvenile idiopathic arthritis according to the associated biologic drug

Adverse events	Anti-TNF-α agents (n=188)	Anti-IL-1 agents (n=12)	Tocilizumab (n=31)
Upper respiratory tract infections, n (%)	2 (1.1)	0 (0)	1 (3.2)
Chickenpox, n (%)	2 (1.1)	0 (0)	0 (0)
Cytomegalovirus, n (%)	0 (0)	1 (8.3)	0 (0)
COVID-19 infection (mild), n (%)	1 (0.5)	0 (0)	0 (0)
Scabies, n (%)	1 (0.5)	0 (0)	0 (0)
Verruca vulgaris, n (%)	2 (1.1)	0 (0)	0 (0)
Parotitis, n (%)	0 (0)	0 (0)	1 (3.2)
Leukopenia, n (%)	0 (0)	0 (0)	1 (3.2)
Low complement levels, n (%)	0 (0)	0 (0)	1 (3.2)
Injection site reactions, n (%)	3 (1.6)	3 (25)	2 (6.4)
Serious adverse events			
Pneumoniae, n (%)	1 (0.5)	0 (0)	1 (3.2)
Preseptal cellulitis, n (%)	1 (0.5)	0 (0)	0 (0)
Lung tuberculosis, n (%)	2 (1.1)	0 (0)	0 (0)
Convulsion and PRES, n (%)	0 (0)	0 (0)	1 (3.2)
Hepatic failure, n (%)	0 (0)	1 (8.3)	0 (0)
Erythematous skin rashes, n (%)	1 (0.5)	2 (16.7)	1 (3.2)
Total, n (%)	16 (8.5)	7 (58.3)	9 (29)

COVID-19: Coronavirus disease-2019, PRES: Posterior reversible encephalopathy syndrome

More AEs were encountered in patients with shorter disease duration at the start of bDMARDs [18.4 (2.2-20.7) vs. 31.3 (8.7-40) months; p=0.002]. There was no significant relationship between AEs and JADAS-71 score at initiation of biologic therapy, additional treatment with a biologic (DMARDs and steroids), total duration of biologic drug usage, age at biologic onset, and the number of previously used biologic therapy.

There was no malignancy or mortality in this cohort.

DISCUSSION

This study showed that although biologic agents increasingly used in children with JIA are highly effective and safe treatments, their side effects should not be underestimated. Rare side effects are reported daily. When planning the treatment management of JIA patients, it seems reasonable and necessary to carefully interpret the benefit-risk balance for each patient.

Anti-TNF drugs are the most effective and first choice bDMARDs for JIA treatment with their effects on pain, stiffness, growth and quality of life (7-10). Currently, etanercept is the most ordered biologic drug for the treatment of JIA. Children and adolescents with JIA are frequently treated with etanercept and an acceptable safety profile over long periods, sometimes even into adulthood (10-12). Prince et al. (11) reported that the most significant improvement occurred in the first 3 months of etanercept treatment and was sustained for a long time in most patients (up to 75 months). In a comprehensive study reporting combined data from nearly 15,000 patients from Pharmachild and national registries [German (BİKeR) and the Swedish registries], methotrexate (61-84%) and etanercept (24-61.8%) were the most used csDMARDs and bDMARDs, respectively (13). Similar to the literature, in our study, the most commonly used biologic drug was TNFi, and the most commonly used biologic drug was etanercept. Also, it was observed that the median (IQR) JADAS-71 was 13 (11-19) at baseline and decreased to 0 (0-2) after a median of 22 (10-40) months of biological treatment.

Placebo-controlled randomized trials of etanercept and adalimumab have not been reported to increase the number of infections during treatment with non-sJIA (14,15), although current evidence from observational studies indicates that infections are the most common AEs (13,16). Also, a large registry-based study (13) demonstrated that infections were the most common AEs (29.4-30.1%), followed by gastrointestinal complaints (11.5-19.6%). In our study, when the patients were evaluated for AEs; it was seen that 27 (11.4%) patients experienced at least one AE. The most common AE was local injection site reactions (n=8) with biologics administered subcutaneously, followed by upper respiratory tract infections (n=4) and diffuse erythematous skin rashes (n=4). The occurrence of AEs was not significantly different between JIA subtypes, similar to the literature (11). However, children with sJIA (35.7%) had the highest risk of AEs due to the injection site reactions commonly seen with anakinra.

Treatments with csDMARDs and bDMARDs in JIA are anticipated to increase the frequency of common infections as well as increase the risk of serious and opportunistic infections such as herpes virus and tuberculosis (16-20). Serious AEs occurred in 6.9% of patients in Pharmachild and in 7.4% of patients in the BiKeR registry (13). SAEs were observed in 11 (4.6%) patients in our cohort. Three of these patients had sJIA using anakinra. Anakinra was discontinued in one patient because of the development of diffuse hypersensitivity reaction and angioedema after the first dose. The clinical course of varicella and herpes zoster in children under immunosuppression is variable. Concomitant CMV infection was detected in a patient under anakinra who developed a diffuse hypersensitivity reaction at the second dose. Two of our patients developed chickenpox not requiring hospitalization after the second dose of TNFi treatment (one patient under etanercept and other under adalimumab). Pneumonia (one patient under etanercept and one patient under tocilizumab) and preseptal cellulitis (under etanercept) requiring hospitalization developed in 3 patients. Two patients developed pulmonary tuberculosis under adalimumab treatment. These patients diagnosed with asymptomatic tuberculosis by repeat screening emphasize the importance of vigilance in tuberculosis screening for all patients under TNFi biologics, particularly in tuberculosis-endemic areas (21).

Although relatively mild liver enzyme elevations are common in the early phase of uncontrolled sJIA, they can also be seen in macrophage activation syndrome. However, when a patient's liver enzymes are initially normal and then increase rapidly and significantly, or in the presence of normal inflammatory markers, other causes should be considered. Liver diseases such as viral or autoimmune hepatitis, Wilson's disease, and drug-induced liver injury are possible etiologies. Severe hepatotoxicity has been reported as a rare side effect of anakinra therapy in patients with sJIA (22,23). One of our patients developed moderate to severe hepatic failure after the 12th dose of anakinra, the patient recovered spontaneously after discontinuation of treatment.

Acute phase reactants are reported to be rapidly reduced with tocilizumab. Although complement proteins are a

component of the acute phase, there are only two case series in the literature that provide information on the potential impact of tocilizumab on complement proteins (24,25). One of our patients in this cohort had low complement, which we noticed in the laboratory examinations we performed after the complaint of hair loss. Nasal ulcers and Raynaud's phenomenon developed during follow-up. Despite the maintenance of reduced complement components, no autoantibody positivity or other clinical signs of immunocomplex disease were seen throughout the 36-month median follow-up. The drop in C3 and C4 serum levels appears to be among the anti-inflammatory effects provided by tocilizumab and can therefore be considered a predicted impact of this medication mechanism of action.

Tocilizumab-associated neurological complications have been reported previously (26-28). In a patient with rheumatoid arthritis developed leukoencephalopathy, a patient with JIA presented with PRES, more recently a patient experienced PRES under tocilizumab as a treatment of giant cell arteritis, and finally, one patient with JIA in our cohort developed PRES after the 50th dose of tocilizumab and could not be explained for any other reason. Therefore, a link between IL-6 and the integrity of the vasculature may be considered. As a result, it seems beneficial to have strict blood pressure monitoring in an outpatient setting in patients receiving tocilizumab.

Uveitis is the most common extra-articular manifestation of JIA. The 2019 American College of Rheumatology recommendations classify patients by JIA subtype, age at diagnosis, duration of disease, and ANA status (29). Although studies have shown that some DMARDs affect uveitis incidence rates, drugs are not currently included in risk stratification guidelines. In our study, 22 (9.3%) patients had uveitis and 8 of them were diagnosed with uveitis at baseline, while 14 patients developed uveitis during follow-up. Six of the 14 patients were on etanercept therapy. The any new cases of uveitis under biologic were by etanercept in our study. We know that etanercept does not cause uveitis, it cannot prevent uveitis's development. This finding agrees with previous studies suggesting that the efficacy of etanercept in the prevention of uveitis is less than that of adalimumab (30-33).

Whether JIA patients have an increased risk of malignancy due to their rheumatic disease or treatment is still controversial. In the literature, an increased risk of malignancy has been reported in children with JIA compared with the general population, regardless of drug use. Conversely, other studies have not confirmed these findings (34-37), and more work is needed to estimate this risk more accurately. There was no malignancy or mortality in our cohort.

One of the important results of our study was that early biologic therapy was initiated in patients with poor prognosis, and AEs were more frequent. Patients with these characteristics should therefore be monitored more closely.

This study is a large cohort that presents a tertiary center experience evaluating the efficacy and safety profile of bDMARDs in patients with JIA. However, it is certain that it has some limitations, such as being a retrospective study, which may lead to inaccurate collection of AEs. Moreover, the relatively small number of some biologic therapy groups and JIA subgroups makes it difficult to interpret statistical analyses between groups. Therefore, multicenter prospective studies are needed to determine real-life data on adverse effects of bDMARDs in JIA.

CONCLUSION

This study supports the view that biological agents are effective in achieving remission by suppressing ongoing inflammation. However, AEs should not be underestimated, and when starting biologic treatment, patients and families should be clearly informed about the possible AEs.

ETHICS

Ethics Committee Approval: This study was approved by the Institutional Review Board of İstanbul University, İstanbul Faculty of Medicine (decision no: 07, date: 08.04.2022).

Informed Consent: Informed consent was obtained from all patients/parents.

Authorship Contributions

Concept: A.T., N.A.A., Design: A.T., N.A.A., Data Collection or Processing: A.T., Analysis or Interpretation: A.T., Literature Search: A.T., N.A.A., Writing: A.T., N.A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
2. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369:767-78.
3. Consolaro A, Ravelli A. Defining criteria for disease activity states in juvenile idiopathic arthritis. Rheumatology (Oxford) 2016;55:595-6.
4. Consolaro A, Giancane G, Schiappapietra B, Davì S, Calandra S, Lanni S, et al. Clinical outcome measures in juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2016;14:23.

5. Wallace CA, Ruperto N, Giannini E; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31:2290-4.
6. Crépin S, Villeneuve C, Merle L. Quality of serious adverse events reporting to academic sponsors of clinical trials: far from optimal. Pharmacoepidemiol Drug Saf 2016;25:719-24.
7. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 2008;58:1496-504.
8. Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis 2013;72:517-24.
9. Schmeling H, Minden K, Foeldvari I, Ganser G, Hospach T, Horneff G. Efficacy and safety of adalimumab as the first and second biologic agent in juvenile idiopathic arthritis: the German Biologics JIA Registry. Arthritis Rheumatol 2014;66:2580-9.
10. Armaroli G, Klein A, Ganser G, Ruehlmann MJ, Dressler F, Hospach A, et al. Long-term safety and effectiveness of etanercept in JIA: an 18-year experience from the BiKeR registry. Arthritis Res Ther 2020;22:258.
11. Prince FH, Twilt M, ten Cate R, van Rossum MA, Armbrust W, Hoppenreijs EP, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. Ann Rheum Dis 2009;68:635-41.
12. Minden K, Niewerth M, Zink A, Seipelt E, Foeldvari I, Girschick H, et al. Long-term outcome of patients with JIA treated with etanercept, results of the biologic register JuMBO. Rheumatology (Oxford) 2012;51:1407-15.
13. Swart J, Giancane G, Horneff G, Magnusson B, Hofer M, Alexeeva [illegible], et al. Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: combined data of more than 15,000 patients from Pharmachild and national registries. Arthritis Res Ther 2018;20:285.
14. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000;342:763-9.
15. Burgos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken) 2015;67:1503-12.
16. Giancane G, Swart JF, Castagnola E, Groll AH, Horneff G, Huppertz HI, et al. Opportunistic infections in immunosuppressed patients with juvenile idiopathic arthritis: analysis by the Pharmachild Safety Adjudication Committee. Arthritis Res Ther 2020;22:71.
17. Becker I, Horneff G. Risk of Serious Infection in Juvenile Idiopathic Arthritis Patients Associated With Tumor Necrosis Factor Inhibitors and Disease Activity in the German Biologics in Pediatric Rheumatology Registry. Arthritis Care Res (Hoboken) 2017;69:552-60.
18. Beukelman T, Xie F, Chen L, Baddley JW, Delzell E, Grijalva CG, et al. Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum 2012;64:2773-80.
19. Beukelman T, Xie F, Baddley JW, Chen L, Delzell E, Grijalva CG, et al. Brief report: incidence of selected opportunistic infections among children with juvenile idiopathic arthritis. Arthritis Rheum 2013;65:1384-9.
20. Horneff G. Biologic-associated infections in pediatric rheumatology. Curr Rheumatol Rep 2015;17:66.
21. Calzada-Hernández J, Anton-López J, Bou-Torrent R, Iglesias-Jiménez E, Ricart-Campos S, Martín de Carpi J, et al. Tuberculosis in pediatric patients treated with anti-TNFα drugs: a cohort study. Pediatr Rheumatol Online J 2015;13:54.
22. Murray GM, Ng SK, Beasley D, Johansen L, Ramanan AV. Severe hepatotoxicity as a rare side effect of anakinra in a patient with systemic JIA. Rheumatology (Oxford) 2021;60:e307-8.
23. Ghuman A, Kumar K, Singh A. 86. Intravenous anakinra treatment in a rare case of macrophage activation syndrome presenting as fulminant liver failure. Rheumatology Advances in Practice 2018;2(suppl_1).
24. Bieber A, Markovits D, Toledano K, Tavor Y, Mader R, Balbir-Gurman A, Braun-Moscovici Y. Hypocomplementemia during tocilizumab treatment: Long-term follow-up results. Medicine (Baltimore) 2022;101:e29528.
25. Romano C, Del Mastro A, Sellitto A, Solaro E, Esposito S, Cuomo G. Tocilizumab reduces complement C3 and C4 serum levels in rheumatoid arthritis patients. Clin Rheumatol 2018;37:1695-700.
26. Butryn M, Mewes S, Feist E, Beuing O, Müller C, Neumann J. Tocilizumab-associated posterior reversible encephalopathy syndrome in giant-cell arteritis - case report. BMC Neurol 2021;21:228.
27. Rosa Júnior M, Borges ÉI, Fonseca APA, Fiorot JL, Balarini L, Valim V. Posterior reversible encephalopathy syndrome during treatment with tocilizumab in juvenile idiopathic arthritis. Arq Neuropsiquiatr 2018;76:720-1.
28. Kobayashi K, Okamoto Y, Inoue H, Usui T, Ihara M, Kawamata J, et al. Leukoencephalopathy with cognitive impairment following tocilizumab for the treatment of rheumatoid arthritis (RA). Intern Med 2009;48:1307-9.
29. Angeles-Han ST, Ringold S, Beukelman T, Lovell D, Cuello CA, Becker ML, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis. Arthritis Care Res (Hoboken) 2019;71:703-16.
30. Davies R, De Cock D, Kearsley-Fleet L, Southwood T, Baildam E, Beresford MW, et al. The risk of uveitis in patients with JIA receiving etanercept: the challenges of analysing real-world data. Rheumatology (Oxford) 2020;59:1391-7.
31. Tappeiner C, Klotsche J, Sengler C, Niewerth M, Liedmann I, Walscheid K, et al. Risk Factors and Biomarkers for the Occurrence of Uveitis in Juvenile Idiopathic Arthritis: Data From the Inception Cohort of Newly Diagnosed Patients With Juvenile Idiopathic Arthritis Study. Arthritis Rheumatol 2018;70:1685-94.
32. Saurenmann RK, Levin AV, Feldman BM, Laxer RM, Schneider R, Silverman ED. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-TNFalpha agents. J Pediatr 2006;149:833-6.
33. Foeldvari I, Becker I, Horneff G. Uveitis Events During Adalimumab, Etanercept, and Methotrexate Therapy in Juvenile Idiopathic Arthritis: Data From the Biologics in Pediatric Rheumatology Registry. Arthritis Care Res (Hoboken) 2015;67:1529-35.
34. Horneff G, Klein A, Oommen PT, Hospach A, Foeldvari I, Feddersen I, et al. Update on malignancies in children with juvenile idiopathic arthritis in the German BIKER Registry. Clin Exp Rheumatol 2016;34:1113-20.
35. Mannion ML, Beukelman T. What is the background incidence of malignancy in children with rheumatic disease? Curr Rheumatol Rep 2013;15:310.
36. Nordstrom BL, Mines D, Gu Y, Mercaldi C, Aquino P, Harrison MJ. Risk of malignancy in children with juvenile idiopathic arthritis not treated with biologic agents. Arthritis Care Res (Hoboken) 2012;64:1357-64.
37. Bernatsky S, Rosenberg AM, Oen KG, Duffy CM, Ramsey-Goldman R, Labrecque J, et al. Malignancies in juvenile idiopathic arthritis: a preliminary report. J Rheumatol 2011;38:760-3.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:276-282
DOI: 10.4274/BMJ.galenos.2023.2023.6-5

Research

Evaluation of Exenatide Versus Insulin Glargine Treatment's Impact on Brown Adipose Tissue Markers and Epicardial Adipose Tissue

Eksenatid ve İnsülin Glargin Tedavisinin Kahverengi Yağ Doku Belirteçleri ve Epikardiyal Yağ Doku Üzerine Etkisinin Karşılaştırmalı Olarak Değerlendirilmesi

Özlem Zeynep Akyay[1], Alev Selek[2], İlhan Tarkun[3], Tayfun Şahin[4], Zeynep Cantürk[2], Berrin Çetinarslan[2], Yağmur Çakmak[5], Canan Baydemir[6]

[1]University of Health Sciences Türkiye, Şanlıurfa Mehmet Akif İnan Training and Research Hospital, Clinic of Endocrinology and Metabolism, Şanlıurfa, Türkiye
[2]Kocaeli University Faculty of Medicine, Department of Endocrinology and Metabolism, Kocaeli, Türkiye
[3]Anadolu Medical Center, Department of Endocrinology and Metabolism, Kocaeli, Türkiye
[4]Kocaeli University Faculty of Medicine, Department of Cardiology, Kocaeli, Türkiye
[5]Kocaeli University Faculty of Medicine, Department of Oncology, Kocaeli, Türkiye
[6]Kocaeli University Faculty of Medicine, Department of Biostatistics and Medical Informatics, Kocaeli, Türkiye

ABSTRACT

Objective: Bone morphogenetic protein-7 (BMP7), unique uncoupling protein-1 (UCP1), PR domain containing 16 (PRDM-16), and irisin are important brown adipose tissue (BAT) markers. This study aimed to evaluate the effects of insulin glargine and exenatide treatment on BAT markers and epicardial adipose tissue (EAT) volume in patients with type 2 diabetes mellitus (T2DM).

Methods: The study included 33 patients with T2DM. Patients with T2DM were randomized to the insulin glargine and exenatide arms. Before and 24 weeks after treatment, serum BAT markers and EAT levels were evaluated and compared in both treatment arms.

Results: EAT decreased in both groups with treatments (both groups $p<0.001$), but there was no significant difference between the two groups when compared. BMP7 significantly decreased with exenatide treatment ($p=0.03$). UCP1 significantly decreased with insulin glargine treatment ($p=0.008$). Pre- and post-treatment percentage changes in irisin, BMP7, UCP1, and PRDM-16 were similiar.

Conclusion: Weight loss and a decrease body fat mass occur with exenatide treatment, but this is probably unrelated to BAT activation.

Keywords: Type 2 diabetes mellitus, BMP7, epicardial adipose tissue, irisin, UCP1, PRDM-16

ÖZ

Amaç: Kemik morfojenik proteini-7 (BMP7), unique uncoupling protein-1 (UCP1), PR domain containing 16 (PRDM-16) ve irisin önemli kahverengi yağ doku (KYD) belirteçlerindendir. Bu çalışma tip 2 diabetes mellitus hastalarında (T2DM) insülin glargin ve eksenatid tedavisinin KYD belirteçleri ve epikardiyal yağ dokusu (EYD) üzerine etkilerini incelemeyi amaçlamıştır.

Gereç ve Yöntem: Çalışmaya 33 T2DM hastası alındı. T2DM hastaları, insülin glargin ve eksenatid kollarına randomize edildi. Her iki tedavi kolunda serum KYD belirteçlerinin ve EYD düzeylerinin tedaviden önce ve tedaviden 24 hafta sonraki verileri değerlendirildi ve karşılaştırıldı.

Bulgular: EYD tedavi ile her iki grupta da azaldı (her iki grupta da $p<0,001$), ancak her iki gruptaki değişimler karşılaştırıldığında aralarında anlamlı fark yoktu. BMP7 eksenatid tedavisi ile anlamlı azaldı ($p=0,03$). UCP1 insülin glargin tedavisi ile anlamlı azaldı ($p=0,008$). İrisin, BMP7, UCP1 ve PRDM-16'nın tedavi öncesi ve tedavi sonrası yüzde değişimleri benzerdi.

Sonuç: Eksenatid tedavisi ile vücut ağırlığında ve total vücut yağında anlamlı azalma oldu ancak bu muhtemelen KYD aktivasyonu bağlı değildi.

Anahtar Kelimeler: Tip 2 diabetes mellitus, BMP7, epikardiyal yağ dokusu, irisin, UCP1, PRDM-16

Address for Correspondence: Özlem Zeynep Akyay, University of Health Sciences Türkiye, Şanlıurfa Mehmet Akif İnan Training and Research Hospital, Clinic of Endocrinology and Metabolism, Şanlıurfa, Türkiye
Phone: +90 505 615 19 42 E-mail: ozlemzeynepakyay@gmail.com ORCID ID: orcid.org/0000-0003-4608-4433

Cite as: Akyay ÖZ, Selek A, Tarkun İ, Şahin T, Cantürk Z, Çetinarslan B, Çakmak Y, Baydemir C. Evaluation of Exenatide Versus Insulin Glargine Treatment's Impact on Brown Adipose Tissue Markers and Epicardial Adipose Tissue. Med J Bakirkoy 2023;19:276-282

Received: 20.06.2023
Accepted: 01.08.2023

INTRODUCTION

The frequency of diabetes and obesity has recently increased (1). Obesity causes insulin resistance, which further results in type 2 diabetes mellitus (T2DM) treatment difficulties. Recently, guidelines have focused on new anti-obesity drug options to break this vicious cycle. Glucagon-like peptide-1 (GLP-1) receptor analogs (GLP-1RAs) are anti-diabetic and anti-obesity drugs that provide a gate to break this vicious cycle by contributing to weight loss. GLP-1RAs exert weight loss effects through various mechanisms, such as central and peripheral effects. Weight loss potentials with brown adipose tissue (BAT) activation have become of particular interest after encouraging initial results (2,3). Humans have three morphological types of adipose tissue: white adipose tissue (WAT), beige adipose tissue, and BAT (4). BAT is an energy-wasting tissue that increases energy expenditure and chemical energy for thermogenesis (5,6). BAT activation can improve metabolic parameters such as hyperglycemia and dyslipidemia, thus making BAT activation a potential therapeutic target for obesity and other metabolic diseases (7,8). BAT contains high mitochondrial density and expresses high levels of uncoupling protein 1 (UCP1). UCP1, which is the most important marker of BAT, is also expressed in human BAT and can regulate thermogenesis (9,10). Bone morphogenic protein-7, PR domain containing 16 (PRDM-16), and irisin are BAT-related markers.

Bone morphogenesis proteins (BMPs) are members of the superfamily of transforming growth factor β (TGF-β). They participate in brown adipocyte development and insulin sensitivity and increase the expression of the PRDM-16. PRDM-16 is a key transcriptional regulator of brown adipose identity (11-13). PRDM-16 induces gene expression in BAT. Irisin is a newly discovered myokine that is secreted in response to exercise (14). Irisin increases PPARα and UCP1 expression, browns WAT (15), improves islet β-cell proliferation (16), and increases energy consumption and thermogenesis of both skeletal muscles and BAT (17).

There are different methods to evaluate BAT, such as 18F-fluorodeoxyglucose positron emission tomography integrated with computed tomography (18F-FDG PET-CT) and magnetic resonance imaging (MRI). Epicardial adipose tissue (EAT) is visceral fat surrounding the pericardium and myocardium; however, its biological characteristics are still not completely known (18). The main marker of BAT is a unique UCP1, which was detected in EAT. Therefore, EAT includes BAT components (19). Studies have shown that the reliability of transthoracic echocardiography (ECHO) in measuring EAT correlates well with MRI (20).

There are studies examining the effect of GLP-1RAs on BAT in animal studies. (3,21-23) However, there are very few human studies on this subject, and they are conflicted (2,24). Insulin glargine is a long-acting basal insulin analog used daily for the treatment of T2DM. To our knowledge, the effect of insulin treatment on BAT has not been investigated in the literature. To our knowledge, the comparative effect of treatment with exenatide versus insulin glargine on the serum levels of irisin, PRDM-16, BMP7, and UCP1 has not been studied.

This study investigated the potential roles of the GLP-1 agonist exenatide on metabolic parameters, EAT value, and serum levels of PRDM-16, irisin, UCP1, and BMP7 by comparing patients with diabetes treated with exenatide with those treated with insulin glargine.

METHODS

Study Design and Participants

This prospective, randomized, active-controlled study was conducted in the Kocaeli University School of Medicine Department of Endocrinology outpatient unit between 2016 and 2019. The study included 33 patients with T2DM. The age of patients with T2DM enrolled in the study was between 18 and 65 years, body mass index (BMI) was 25-35 kg/m^2, with hemoglobin A1c (HbA1c) >7% and <10%, who were on metformin 2×1 g/day alone in stable dose for at least 3 months during enrollment. Renal or hepatic impairment, thyroid dysfunction, coronary artery disease, cardiac failure, infectious or inflammatory disease, cancer and pregnancy was exclusion criteria. In addition, patients on insulin- or incretin-based therapy and patients with acute or chronic pancreatic disease were excluded from the study.

Patients with T2DM were randomized one to one to the exenatide or insulin glargine arm to investigate the effects of exenatide and insulin glargine treatment on BAT markers (irisin, PRDM-16, UCP1, and BMP7) and EAT. Twenty patients were included in the exenatide arm and 20 patients in the insulin glargine arm. Exenatide treatment was administered as 5 μg SC for the first month and titrated to 10 μg SC for the next 5 months. Insulin glargine was started at 0.2 IU/kg at night, and the dose was titrated according to fasting blood glucose levels. 0-, 4-, 12-, and 24-week visits of the patients were performed. Physical examinations, including vital signs and examination of all systems, were performed during these visits, and drug side effects were questioned. Height, weight, and BMI measurements were taken, and routine biochemistry tests were performed at 0- and 24-week visits. Blood samples for irisin, PRDM-16, UCP1, and BMP7 were collected. ECHO measured EAT at 0- and 24-

week visits. In the insulin glargine arm, two patients left the study because they wanted to stop injection therapy, and two patients were lost to follow-up. In the exenatide arm, two patients were excluded because of the side effect of vomiting, and one patient was lost follow-up. The insulin glargine arm was completed with 16 patients, and the arm with 17 patients. Pre- and post-treatment biochemical parameters, irisin, PRDM-16, UCP1, BMP7, and EAT levels were compared in both T2DM groups.

This study was approved by the Kocaeli University Non-Invasive Clinical Research Ethics Committee (decision no: KÜ GOKAEK 2017/820, project no: 2017/160, date: 07.06.2017). All experiments were conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Biochemical Analysis

Blood samples were collected at 0 and 24 weeks after 8-10 hours (h) of fasting at 09.00 in the morning. Serum was obtained, and centrifuged blood samples were stored at -80 °C until analysis. The concentrations of UCP1, irisin, PRDM-16, and BMP7 were analyzed using a Radim Diagnostics Rome (Italy) device with a sandwich enzyme-linked immunosorbent assay method in accordance with the manufacturer's instructions (Elabscience).

Body Weight and Total Body Fat Mass Assessment

Body weight and total body fat mass were measured using the bioimpedance analysis technique with the Tanita BC-418 body composition analyzer device.

Baseline Echocardiography and Assessment of the Epicardial Adipose Tissue Thickness

All cases were evaluated with conventional ECHO in the left lateral decubitus position using a commercially available system (VIVID 7, General Electric-Vingmed Ultrasound, Horten, Norway). Measurements were performed by an experienced cardiologist blindly. EAT appeared as an echo-free space in the pericardial layers on a two-dimensional ECHO and was measured on the free wall of the right ventricle from a parasternal long-axis view, using the aortic annulus as an anatomic reference. EAT was measured perpendicularly in front of the right ventricular free wall at end-systole (20,25). The average value of three cardiac cycles was calculated.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 23.0 (IBM SPSS Inc., Chicago, IL). The conformity of the variables to the normal distribution was examined visually (histogram and probability graphs) using the Shapiro-Wilk test. Descriptive data are presented as median and maximum-minimum values (median and minimum-maximum) for non-normally distributed variables and as mean and standard deviation for normally distributed data. The Mann-Whitney U test was used for independent variables, and the Wilcoxon signed-rank test was used for dependent variables to compare the numerical values of the two groups that were found to be non-normally distributed. An independent t-test was used for independent variables, and a paired t-test was used for dependent variables to compare the numerical values of the two groups that were found to have a normal distribution. The results were accepted as a 95% confidence interval, statistical significance $p<0.05$.

RESULTS

The demographic data, pre- and post-treatment biochemical parameters of the exenatide and insulin glargine groups are summarized in Table 1. The exenatide and insulin glargine groups were similar in terms of age, gender, age of diabetes, BMI, glucose, and HbA1c level. HbA1c levels significantly decreased after treatment in both groups; also, the pre- and post-treatment changes of HbA1c were similar between groups.

Effect on the Body Mass Index and Total Body Fat Mass

There was a significant reduction in BMI and total body fat mass with treatment in the exenatide group compared with glargine ($p<0.001$; $p=0.01$, respectively).

Effect on the Epicardial Adipose Tissue

The impact of exenatide versus insulin glargine treatment on EAT is shown in Table 2. EAT levels significantly decreased in both treatment groups. However, EAT differences were similar between the groups.

Effect on Brown Adipose Tissue Markers

The impact of exenatide versus insulin glargine treatment on BAT markers is shown in Table 2. Pre- and post-treatment serum irisin and PRDM-16 levels were similar in both treatment arms. BMP7 significantly decreased with exenatide treatment ($p=0.03$). UCP1 significantly decreased with insulin glargine treatment ($p=0.008$). Pre- and post-treatment percentage changes in irisin, BMP7, UCP1, and PRDM-16 were not significantly different between the groups.

DISCUSSION

In this study, although there was a significant improvement in BMI and total body fat mass with exenatide compared with insulin glargine treatment in patients with T2DM, no

Table 1. The demographic data, pre-, and post-treatment biochemical parameters of the exenatide and insulin glargine groups

Variables	Exenatide group (n=17)	Glargine group (n=16)	p-value
Age (years)	49.88±7.76	51.25±6.95	0.599
Gender (female/male)	15/2	10/6	0.095
DM age (years)	4.58±3.89	6.37±4.14	0.211
BMI (kg/m^2)-$_{pre}$	37.47±4.47	35.27±1.92	0.079
BMI (kg/m^2)-$_{post}$	35.89±4.71	35.23±1.76	0.605
p-value	**<0.001**	0.76	
Change from baseline (%)	-3.42 (-8.01 to -1.24)	0.13 (-0.81 to 0.5)	**<0.001**
Total body fat mass (kg)-$_{pre}$	40.72±10.38	35.71±5.60	0.100
Total body fat mass (kg)-$_{post}$	40.37.55±11.50	35.06±5.73	0.103
p-value	**<0.001**	0.06	
Change from baseline (%)	-9.11 (-13.17 to -3.49)	-0.72 (-5.93 to 0,56)	**0.01**
Glucose-$_{pre}$ (mg/dL)	147.52±39.44	142.81±15.83	0.656
Glucose-$_{post}$ (mg/dL)	132.29±36.08	114±18.15	0.093
p-value	0.02	**<0.001**	
Change from baseline (%)	-13.04 (-17.57 to -1.43)	-20.53 (-24.11 to -14.59)	**0.03**
Triglyceride-$_{pre}$ (mg/dL)	160.11±71.62	124.87±63.36	0.145
Triglyceride-$_{post}$ (mg/dL)	202.11±100.15	157.87±91.02	0.195
p-value	0.03	0.02	
Change from baseline (%)	22.5 (-8.19 to 58.5)	3.16 (0.00 to 55.64)	1.00
Total cholesterol-$_{pre}$ (mg/dL)	176.23±31.59	193.75±37.34	0.155
Total cholesterol-$_{post}$ (mg/dL)	191.23±21.60	187.46±29.00	0.677
p-value	0.085	0.39	
Change from baseline (%)	4.32 (-4.95 to31.97)	0.00 (-6.25 to 1.65)	0.26
LDL cholesterol-$_{pre}$ (mg/dL)	102.27±30.03	129.05±32.91	0.020
LDL cholesterol-$_{post}$ (mg/dL)	106.91±18.92	116.82±33.29	0.298
p-value	0.52	0.17	
Change from baseline (%)	-3.42 (-9.71 to 41.33)	-0.25 (-8.82 to 0.00)	0.65
HDL cholesterol-$_{pre}$ (mg/dL)	42.47±8.70	46.00±8.35	0.244
HDL cholesterol-$_{post}$ (mg/dL)	44.58±8.29	45.68±9.20	0.721
p-value	0.23	0.74	
Change from baseline (%)	0.00 (-5.4 to 12.07)	0.00 (-4.19 to 5.27)	0.53
HbA1c-$_{pre}$ (%)	8.43±0.99	8.10±0.45	0.236
HbA1c-$_{post}$ (%)	7.23±1.25	7.11±0.46	0.730
p-value	**0.002**	**≤0.001**	
Change from baseline (%)	-8.57 (-26.42 to -1.50)	-11.60 (-18.13 to -4.42)	1.00

Data was given as mean ± standard deviation or median (minimum-maximum) depending on the distribution.
DM: Diabetes mellitus, BMI: Body mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TSH: Thyroid-stimulating hormone, HbA1c: hemoglobin A1c

Table 2. Exenatide versus insulin glargine treatment's impact on EAT and brown adipose tissue markers

Variables	Exenatide group (n=17)	Glargine group (n=16)	p-value
PRDM-16-$_{pre}$	239.29±106.10	227.43±80.88	0.722
PRDM-16$_{-post}$	232.18±69.75	277.62±194.32	0.386
p-value	0.8	0.2	
Change from baseline (%)	-5.16 (-14.62 to 20)	9.94 (-16.96 to 54.45)	0.32
Irisin-$_{pre}$ (pg/mL)	6.62±3.37	5.71±2.49	0.386
Irisin$_{-post}$ (pg/mL)	6.09±3.48	5.84±2.84	0.820
p-value	0.2	0.4	
Change from baseline (%)	-3.07 (-23.11 to 6.48)	12.5 (-13.76 to 19.77)	0.16
UCP1-$_{pre}$ (ng/mL)	1.79±0.89	2.22±1.18	0.241
UCP1$_{-post}$ (ng/mL)	1.26±0.48	1.13±0.73	0.570
p-value	0.06	**0.008**	
Change from baseline (%)	-30.97 (-55.10 to 54.54)	-36.18 (-77.19 to 6.73)	0.23
BMP7-$_{pre}$ (pg/mL)	213.85±100.75	195.55±90.31	0.587
BMP7$_{-post}$ (pg/mL)	139.69±45.81	153.30±120.37	0.667
p-value	**0.03**	0.14	
Change from baseline (%)	-27.96 (-59.10 to 38.29)	-21.27 (-69.07 to 28.76)	0.87
EAT-$_{pre}$ cm	0.61±0.15	0.71±0.14	0.176
EAT-$_{post}$ cm	0.48±0.12	0.56±0.15	0.140
p-value	**0.000**	**0.000**	
Change from baseline (%)	-20 (-30.95 to -16.66)	-22.5 (-32.14 to -11.45)	0.81

Data was given as mean ± standard deviation or median (minimum-maximum) depending on the distribution.
Pre: Pretreatment, post: Post-treatment, PRDM-16: PR domain containing 16, UCP-1: Unique uncoupling protein 1, BMP-7: Bone morphogenetic protein 7, EAT: Epicardial adipose tissue

significant difference was observed between the groups in posttreatment BAT markers. EAT decreased in both treatment groups, but there was no significant difference between the two groups.

Brown fat mass in adults is positively related to weight loss and metabolic health (26,27) and can be activated (28). In a recent study, which compared liraglutide and placebo, BAT was measured from the supraclavicular fat depot using MRI, and no difference was found between the two groups. In this study, the GLP-1 agonist did not affect the activation of BAT, and a decreasing or changing supraclavicular fat store reflecting BAT was not observed (29). We evaluated BAT containing EAT using ECHO, and EAT decreased after exenatide and insulin glargine treatment. However, there was no significant change in EAT when the two groups were compared. Similar to our study, other studies have shown that EAT decreased with insulin glargine and exenatide treatment (30,31). In contrast to our study, Janssen et al. (32) studied the effects of exenatide treatment weekly in 24 patients who were not obese and without diabetes. They found that exenatide increased the volume and FDG uptake in cervical and supraclavicular upper mediastinal, axillary, and paravertebral BAT depots by 18-F FDG PET-CT. However, the same result was not achieved when they evaluated the supraclavicular region using MRI. The reason we could not obtain similar results may be that we evaluated a different BAT region or that our patients were diabetic.

UCP1 is a mitochondrial inner membrane protein considered as a marker of BAT activity and is significantly expressed in BAT. Wan et al. (33) reported that chronic peripheral treatment with the GLP-1R agonist supaglutide upregulates the expression of UCP1 in inguinal WAT, not in BAT and epididymal WAT. An animal study concluded that GLP-1 agonists did not affect UCP1 expression in BAT. They put forward that the GLP-1 agonist does not increase thermogenesis (24). In line with these studies, in our study, UCP1 differences were similar between the two treatment arms. In contrast to our study, a previous study showed that centrally administered liraglutide increases UCP1 expression in mice in BAT and WAT (2).

Irisin secreted in response to exercise is a newly discovered myokine. Animal studies have shown that irisin modulates energy metabolism (14). Serum irisin levels significantly increased after exenatide treatment in the study by Liu et al. (34). In our study, irisin differences were similar in the exenatide and glargine treatment groups. In Liu et al.'s study (34), exenatide treatment was used as the initial treatment for diabetes. In our study, both the exenatide and glargine groups used metformin as the initial treatment. Animal and human studies have shown that metformin increases serum irisin (35,36). Therefore, the use of metformin may be the reason why we cannot achieve improvement in the irisin level.

BMPs are members of the TGF-β superfamily (37). BMPs, especially BMP4, BMP7, and BMP8, can participate in the process of brown adipocyte development and the differentiation of white adipocytes to brown adipocytes (12). A rat study showed that BMP7 gene expression increased after GLP-1 agonist treatment (38). There has been no study on levels of BMP7 in patients receiving GLP-1 agonist therapy in humans. In this study, BMP7 levels significantly decreased with exenatide treatment, but BMP7 differences were not significant between the treatment groups. BMP7 increases the expression of PRDM-16, providing a balance between brown fat and skeletal muscle change (39,40). GLP-1 agonists increased the activity of insulin-suppressing lipolysis in subcutaneous adipose tissue (41). However, the benefits of GLP-1 agonists in BAT have not been clearly understood (42). A study on mice showed that GLP-1 agonist therapy increased both UCP1 and PRDM-16 expression in skeletal muscle but not in perigonadal fat (43). So far, we noticed no study on serum levels of PRDM-16 in patients with diabetes or related to GLP-1 agonist therapy in humans. Our results showed that the pre- and post-treatment serum PRDM-16 differences were similar in both treatment arms.

The limitations of our study are a relatively low number of participants, differences in the duration of follow-up, and the non-assessment of the time of physical activity and caloric intake. The absence of 4 and 8 weeks of evaluation was another limitation. In some studies evaluating REE, the REE increment seen in the first week were not seen in further weeks. It has been suggested that this was a mechanism to limit weight loss (29,44,45). Unfortunately, as we did not evaluate the first-week markers, we may have missed the increment. However, a longer treatment duration may be needed for further activation of BAT. Another reason for nonactivated BAT may be the different seasonal activation of BAT. We evaluated the results of the participants at 24 weeks in different seasons; as BAT is cold activated (26,46), seasonal changes may affect our results.

CONCLUSION

Weight loss and a decrease body fat mass occur with exenatide treatment, but this is probably not related to BAT activation. The effects of GLP-1s on BAT in humans are controversial. More comprehensive studies are needed with more patients and longer follow-up periods to clarify this situation.

Acknowledgments: Preparation for publication of this article is supported by the Society of Endocrinology and Metabolism of Türkiye.

ETHICS

Ethics Committee Approval: Pre-study ethics committee approval was received from Kocaeli University Medical School Clinical Research Ethics Committee. Ethics committee project no is KÜ GOKAEK 2017/160 (decision no: KÜ GOKAEK 2017/820, date: 07.06.2017).

Informed Consent: Written consent was obtained from all patients or their relatives.

Authorship Contributions

Surgical and Medical Practices: Ö.Z.A., A.S., Y.Ç., Concept: Ö.Z.A., İ.T., Z.C., Y.Ç., Design: Ö.Z.A., İ.T., Y.Ç., Data Collection or Processing: Ö.Z.A., İ.T., B.Ç., Y.Ç., Analysis or Interpretation: T.Ş., C.B., Literature Search: Ö.Z.A., A.S., İ.T., Writing: Ö.Z.A., A.S., B.Ç., Y.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by Kocaeli University Scientific Research Projects Unit (KOU 2017/196).

REFERENCES

1. IDF Diabetes Atlas. 9th edition. 2019. Available from: URL: https://diabetesatlas.org/atlas/ninth-edition/
2. Beiroa D, Imbernon M, Gallego R, Senra A, Herranz D, Villarroya F, et al. GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK. Diabetes 2014;63:3346-58.
3. Horowitz M, Flint A, Jones KL, Hindsberger C, Rasmussen MF, Kapitza C, et al. Effect of the once-daily human GLP-1 analogue liraglutide on appetite, energy intake, energy expenditure and gastric emptying in type 2 diabetes. Diabetes Res Clin Pract 2012;97:258-66.
4. Chait A, den Hartigh LJ. Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease. Front Cardiovasc Med 2020;7:22.
5. Li Y, Fromme T. Uncoupling Protein 1 Does Not Produce Heat without Activation. Int J Mol Sci 2022;23:2406.
6. Crichton PG, Lee Y, Kunji ER. The molecular features of uncoupling protein 1 support a conventional mitochondrial carrier-like mechanism. Biochimie 2017;134:35-50.
7. McNeill BT, Suchacki KJ, Stimson RH. MECHANISMS IN ENDOCRINOLOGY: Human brown adipose tissue as a therapeutic target: warming up or cooling down? Eur J Endocrinol 2021;184:R243-59.

8. Leitner BP, Huang S, Brychta RJ, Duckworth CJ, Baskin AS, McGehee S, et al. Mapping of human brown adipose tissue in lean and obese young men. Proc Natl Acad Sci U S A 2017;114:8649-54.
9. Sharp LZ, Shinoda K, Ohno H, Scheel DW, Tomoda E, Ruiz L, et al. Human BAT possesses molecular signatures that resemble beige/brite cells. PLoS One 2012;7:e49452.
10. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, et al. Functional brown adipose tissue in healthy adults. N Engl J Med 2009;360:1518-25. Erratum in: N Engl J Med 2009;361:1123.
11. Cheng L, Wang J, Dai H, Duan Y, An Y, Shi L, et al. Brown and beige adipose tissue: a novel therapeutic strategy for obesity and type 2 diabetes mellitus. Adipocyte 2021;10:48-65.
12. Hogan BL. Bone morphogenetic proteins: multifunctional regulators of vertebrate development. Genes Dev 1996;10:1580-94.
13. Seale P, Kajimura S, Yang W, Chin S, Rohas LM, Uldry M, et al. Transcriptional control of brown fat determination by PRDM16. Cell Metab 2007;6:38-54.
14. Huh JY, Mougios V, Kabasakalis A, Fatouros I, Siopi A, Douroudos II, et al. Exercise-induced irisin secretion is independent of age or fitness level and increased irisin may directly modulate muscle metabolism through AMPK activation. J Clin Endocrinol Metab 2014;99:E2154-61.
15. Zhang Y, Li R, Meng Y, Li S, Donelan W, Zhao Y, et al. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. Diabetes 2014;63:514-25.
16. Sanchis-Gomar F, Perez-Quilis C. The p38-PGC-1α-irisin-betatrophin axis: Exploring new pathways in insulin resistance. Adipocyte 2014;3:67-8.
17. Rodríguez A, Becerril S, Ezquerro S, Méndez-Giménez L, Frühbeck G. Crosstalk between adipokines and myokines in fat browning. Acta Physiol (Oxf) 2017;219:362-81.
18. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J 2007;153:907-17.
19. Sacks HS, Fain JN, Holman B, Cheema P, Chary A, Parks F, et al. Uncoupling protein-1 and related messenger ribonucleic acids in human epicardial and other adipose tissues: epicardial fat functioning as brown fat. J Clin Endocrinol Metab 2009;94:3611-5.
20. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11:304-10.
21. Harder H, Nielsen L, Tu DT, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. Diabetes Care 2004;27:1915-21.
22. van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. Int J Obes (Lond) 2014;38:784-93.
23. Kooijman S, Wang Y, Parlevliet ET, Boon MR, Edelschaap D, Snaterse G, et al. Central GLP-1 receptor signalling accelerates plasma clearance of triacylglycerol and glucose by activating brown adipose tissue in mice. Diabetologia 2015;58:2637-46.
24. Stanford KI, Middelbeek RJ, Townsend KL, An D, Nygaard EB, Hitchcox KM, et al. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. J Clin Invest 2013;123:215-23.
25. Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003;88:5163-8.
26. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, et al. Cold-activated brown adipose tissue in healthy men. N Engl J Med 2009;360:1500-8. Erratum in: N Engl J Med 2009;360:1917.
27. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009;360:1509-17.
28. Cypess AM, Chen YC, Sze C, Wang K, English J, Chan O, et al. Cold but not sympathomimetics activates human brown adipose tissue in vivo. Proc Natl Acad Sci U S A 2012;109:10001-5.
29. van Eyk HJ, Paiman EHM, Bizino MB, IJzermans SL, Kleiburg F, Boers TGW, et al. Liraglutide decreases energy expenditure and does not affect the fat fraction of supraclavicular brown adipose tissue in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis 2020;30:616-24.
30. Elisha B, Azar M, Taleb N, Bernard S, Iacobellis G, Rabasa-Lhoret R. Body Composition and Epicardial Fat in Type 2 Diabetes Patients Following Insulin Detemir Versus Insulin Glargine Initiation. Horm Metab Res 2016;48:42-7.
31. Dutour A, Abdesselam I, Ancel P, Kober F, Mrad G, Darmon P, et al. Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy. Diabetes Obes Metab 2016;18:882-91.
32. Janssen LGM, Nahon KJ, Bracké KFM, van den Broek D, Smit R, Sardjoe Mishre ASD, et al. Twelve weeks of exenatide treatment increases [18F]fluorodeoxyglucose uptake by brown adipose tissue without affecting oxidative resting energy expenditure in nondiabetic males. Metabolism 2020;106:154167.
33. Wan Y, Bao X, Huang J, Zhang X, Liu W, Cui Q, et al. Novel GLP-1 Analog Supaglutide Reduces HFD-Induced Obesity Associated with Increased Ucp-1 in White Adipose Tissue in Mice. Front Physiol 2017;8:294.
34. Liu J, Hu Y, Zhang H, Xu Y, Wang G. Exenatide treatment increases serum irisin levels in patients with obesity and newly diagnosed type 2 diabetes. J Diabetes Complications 2016;30:1555-9.
35. Li M, Yang M, Zhou X, Fang X, Hu W, Zhu W, et al. Elevated circulating levels of irisin and the effect of metformin treatment in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2015;100:1485-93. Erratum in: J Clin Endocrinol Metab 2015;100:3219.
36. Li DJ, Huang F, Lu WJ, Jiang GJ, Deng YP, Shen FM. Metformin promotes irisin release from murine skeletal muscle independently of AMP-activated protein kinase activation. Acta Physiol (Oxf) 2015;213:711-21.
37. Vukicevic S, Basic V, Rogic D, Basic N, Shih MS, Shepard A, et al. Osteogenic protein-1 (bone morphogenetic protein-7) reduces severity of injury after ischemic acute renal failure in rat. J Clin Invest 1998;102:202-14.
38. Ramzy MM, Abdalla AM, Zenhom NM, Okasha AM, Abdelkafy AE, Saleh RK. Therapeutic effect of liraglutide on expression of CTGF and BMP-7 in induced diabetic nephropathy. J Cell Biochem 2019;120:17512-9.
39. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nat Med 2013;19:1252-63.
40. Harms MJ, Ishibashi J, Wang W, Lim HW, Goyama S, Sato T, et al. Prdm16 is required for the maintenance of brown adipocyte identity and function in adult mice. Cell Metab 2014;19:593-604.
41. Armstrong MJ, Hull D, Guo K, Barton D, Hazlehurst JM, Gathercole LL, et al. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. J Hepatol 2016;64:399-408.
42. Heppner KM, Marks S, Holland J, Ottaway N, Smiley D, Dimarchi R, et al. Contribution of brown adipose tissue activity to the control of energy balance by GLP-1 receptor signalling in mice. Diabetologia 2015;58:2124-32.
43. Zhou JY, Poudel A, Welchko R, Mekala N, Chandramani-Shivalingappa P, Rosca MG, et al. Liraglutide improves insulin sensitivity in high fat diet induced diabetic mice through multiple pathways. Eur J Pharmacol 2019;861:172594.
44. Doré C, Hesp R, Wilkins D, Garrow JS. Prediction of energy requirements of obese patients after massive weight loss. Hum Nutr Clin Nutr 1982;36C:41-8.
45. Kiortsis DN, Durack I, Turpin G. Effects of a low-calorie diet on resting metabolic rate and serum tri-iodothyronine levels in obese children. Eur J Pediatr 1999;158:446-50.
46. Au-Yong IT, Thorn N, Ganatra R, Perkins AC, Symonds ME. Brown adipose tissue and seasonal variation in humans. Diabetes 2009;58:2583-7.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:283-286
DOI: 10.4274/BMJ.galenos.2023.2023.6-2

Research

Examining Biomarker Levels in Patients Diagnosed with Multiple Sclerosis

Multiple Skleroz Tanılı Hastalarda Biomarker Düzeylerinin İncelenmesi

İbrahim Acır[1], Abbas Musa Yılmaz[2], Alperen Güngör[2], Yusuf Çevik[2], Esra Derya Dinç Polat[1], Vildan Yayla[1]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Neurology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

Objective: Multiple sclerosis (MS) is a chronic autoimmune disorder characterized by inflammation, demyelination, and axonal damage in the central nervous system. Oligoclonal bands (OCBs) composed of immunoglobulin G (IgG) antibodies in the cerebrospinal fluid (CSF) are a key diagnostic marker for MS, indicating intrathecal IgG synthesis. Recent research has emphasized the importance of distinguishing between kappa and lambda light chains in understanding the clinical implications of OCBs in MS. This study aimed to explore the relationship between kappa light chain and clinical findings, considering the presence and type of OCBs in MS.

Methods: A total of 72 MS patients were included, and their demographic characteristics, laboratory results, CSF analysis, and cranial/spinal magnetic resonance imaging findings were recorded. Blood samples were collected for kappa light chain analysis. The presence of spinal lesions, kappa light chain level, Expanded Disability Status scale (EDSS) score, and IgG index were compared among patients based on OCB positivity type.

Results: The mean age of 72 MS patients was 38.6±10.2 spinal lesions were in 41 patients. The free kappa LC level was calculated as 15.2 mg/L (8.8-48.6), and the serum kappa LC level was 2.8 mg/L (1.5-7.3). No significant relationship was observed between free and serum kappa light chain levels, IgG index, EDSS score, spinal lesion count, and total lesion count in patients with OCB types 1 and 2. In addition, subgroup analysis among patients with OCB type 2 revealed no significant relationship.

Conclusion: In this study, no relationship was found between the EDSS score and free kappa light chain. Although other studies have shown a correlation between the number of spinal lesions and kappa light chain levels, no such correlation was observed in this study. Understanding the specific role of the kappa light chain in MS can provide insights into disease severity, clinical subtypes, and treatment response. Such knowledge can contribute to personalized treatment approaches and improved prognosis for MS patients.

Keywords: Kappa light chain, oligoclonal band, multiple sclerosis

ÖZ

Amaç: Multipl skleroz (MS), merkezi sinir sisteminde enflamasyon, demiyelinizasyon ve akson hasarı ile karakterize kronik otoimmün bir bozukluktur. Beyin omurilik sıvısında (BOS) bulunan immünoglobulin G (IgG) antikorlarından oluşan oligoklonal bantlar (OCB'ler), MS için önemli bir belirteç olup intratekal IgG sentezini göstermektedir. Son araştırmalar, MS'deki OCB'lerin klinik sonuçlarını anlamak için kappa ve lambda hafif zincirler arasındaki ayrımın önemini vurgulamıştır. Bu çalışma, MS'deki OCB'lerin varlığı ve tipini dikkate alarak kappa hafif zincir ile klinik bulgular arasındaki ilişkiyi araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Toplam 72 MS hastası dahil edildi ve demografik özellikleri, laboratuvar sonuçları, BOS analizi ve kraniyal/spinal manyetik rezonans görüntüleme bulguları kaydedildi. Kappa hafif zincir analizi için kan örnekleri alındı. OCB pozitifliği tipine göre hastalar arasında spinal lezyonların varlığı, kappa hafif zincir seviyesi, Genişletilmiş Sakatlık Durumu ölçeği (EDSS) skoru ve IgG indeksi karşılaştırıldı.

Bulgular: Yetmiş iki MS hastasının ortalama yaşı 38,6±10,2 idi. Kırk bir hastada spinal lezyonlar mevcuttu. Serbest kappa hafif zincir seviyesi 15,2 mg/L (8,8-48,6) olarak hesaplandı ve serum kappa hafif zincir seviyesi 2,8 mg/L (1,5-7,3) idi. OCB tipi 1 ve 2 olan hastalarda serbest ve serum kappa hafif zincir seviyeleri, IgG indeksi, EDSS skoru, spinal lezyon sayısı ve toplam lezyon sayısı arasında anlamlı bir ilişki gözlenmedi. Ayrıca, OCB tipi 2 olan hastalar arasında yapılan alt grup analizinde anlamlı bir ilişki bulunmadı.

Address for Correspondence: İbrahim Acır, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Neurology, İstanbul, Türkiye
Phone: +90 544 449 86 78 E-mail: iacir33@gmail.com ORCID ID: orcid.org/0000-0002-9650-8022

Cite as: Acır İ, Yılmaz AM, Güngör A, Çevik Y, Dinç Polat ED, Yayla V. Examining Biomarker Levels in Patients Diagnosed with Multiple Sclerosis. Med J Bakirkoy 2023;19:283-286

Received: 16.06.2023
Accepted: 18.08.2023

Sonuç: Bu çalışmada, EDSS skoru ile serbest kappa hafif zincir arasında bir ilişki bulunmadı. Diğer çalışmalar, spinal lezyon sayısı ile kappa hafif zincir seviyeleri arasında bir korelasyon göstermiş olsa da, bu çalışmada böyle bir korelasyon gözlenmedi. MS'deki kappa hafif zincirin özel rolünün anlaşılması, hastalık şiddeti, klinik alt tipler ve tedavi yanıtı konusunda bilgi sağlayabilir. Bu tür bilgi, kişiselleştirilmiş tedavi yaklaşımlarına ve MS hastaları için iyileştirilmiş prognoza katkıda bulunabilir.

Anahtar Kelimeler: Kappa hafif zincir, oligoklonal band, multipl skleroz

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disorder affecting the central nervous system, characterized by inflammation, demyelination, and axonal damage. One of the key diagnostic markers for MS is the presence of oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF) (1). OCBs are composed of immunoglobulin G (IgG) antibodies, and their presence suggests intrathecal IgG synthesis. However, recent research has highlighted the importance of differentiating between kappa and lambda light chains in understanding the clinical implications of OCBs in MS.

OCBs are detected through immunofixation or isoelectric focusing of CSF, and their presence is considered a valuable diagnostic criterion for MS. OCBs are found in approximately 80-95% of MS patients, indicating a specific immune response within the central nervous system. OCBs arise from the clonal expansion of B cells and subsequent production of specific IgG antibodies. These antibodies, along with the involved B cells, are believed to play a role in the inflammatory cascade observed in MS (2).

The Ig molecule consists of two heavy chains and two light chains, which can be further classified into two types: kappa and lambda. Recent studies have shown that analyzing the composition of OCBs by distinguishing between kappa and lambda light chains can provide additional insights into the pathophysiology of MS (3).

This article aims to explore the relationship between the kappa light chain and clinical findings, considering the presence and type of OCBs in MS.

METHODS

A total of 72 patients diagnosed with MS were included in this study. Demographic characteristics, laboratory results, and CSF analysis results of the patients were recorded. During the patients' last outpatient follow-ups, cranial and spinal magnetic resonance imagings (MRI) were performed according to the MS protocol. The Kappa light chain was studied from the blood samples obtained from the patients simultaneously with MRI. The number of cranial and spinal lesions was calculated and compared with the blood and CSF results. The presence of OCBs was classified as type 1 or type 2 positivity. One patient with type 3 positivity was included in the number of type 2 positive patients. The presence of spinal lesions, kappa light chain level, EDSS level, and IgG index were compared among patients based on the OCB positivity type.

Statistical Analysis

Statistical analyzes were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) software. The normal distribution of the data was evaluated using the Shapiro-Wilk test. Numerical variables showing a normal distribution and those not showing a normal distribution are presented as mean ± standard deviation and median (minimum-maximum), respectively. Categorical variables are expressed as numbers and percentages. The levels of free and serum kappa-LC did not follow a normal distribution, and differences between groups were evaluated using the Mann-Whitney U test or Kruskall-Wallis H test (post-hoc: Dunn's test). The relationship between the numerical variables was examined using Spearman correlation analyzes $p<0.05$ was considered statistically significant.

Informed consent forms were obtained from all the participating patients. University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee approval was obtained using protocol number 2022/191 and decision number 2022-12-03 (date: 20.06.2022).

RESULTS

Of the 72 evaluated MS patients, 51 were female and 21 were male. The mean age was 38.6±10.2. Among the patients, 52 had relapsing-remitting MS (RRMS), 10 had secondary progressive MS (SPMS), 5 had radiologically isolated syndrome, 4 had primary progressive MS (PPMS), and 1 patient had clinically isolated syndrome (Table 1).

Twenty two patients were receiving interferon treatment. Fourteen patients were using fingolimod, 13 patients were on glatiramer acetate, 6 patients were taking teriflunomide, 6 patients were receiving okrelizumab, 4 patients were on dimethyl fumarate, and 1 patient was using azathioprine. Six patients were being followed without any treatment.

Spinal lesions were in 41 patients. One patient had lesions in the thoracic area, whereas cervical spinal lesions were in

all 40 patients. The free kappa LC level was calculated as 15.2 mg/L (8.8-48.6), and the serum kappa LC level was 2.8 mg/L (1.5-7.3) (Table 1).

No significant relationship was observed between the levels of free and serum kappa-LC, IgG index, EDSS score, spinal lesion count, and total lesion count in patients with OCB types 1 and 2. Additionally, in the subgroup analysis conducted among patients with OCB type 2, no significant relationship was found (Table 2).

DISCUSSION

The presence of OCBs has been associated with a more severe disease course in MS (4). Specifically, a higher number of OCBs has been linked to increased disability progression and a higher risk of transitioning from RRMS to SPMS. However, the impact of the kappa light chain specifically on disease severity requires further investigation. In our study, no relationship was detected between OCB positivity (type 2 pattern) and free kappa light chain. In a previous study, it was stated that kappa free light chain levels have an additive predictive value for early MS disease activity that is independent of known predictors (5). On the contrary, our findings suggest that the level of kappa light chains may not be as decisive in indicating disease severity as OCB positivity.

Some studies have suggested that the presence of kappa light chains is more frequently associated with PPMS and SPMS, which are generally characterized by a progressive disease course compared with RRMS (6). This observation indicates that the kappa light chain may be associated with a more progressive and disabling form of MS. In our study, no relationship was found between the patients' EDSS and free kappa light chain. This finding suggests that EDSS alone may not be sufficient to determine disease severity.

The number of spinal lesions in MS can have varying degrees of severity and can impact the overall disease progression and clinical presentation (7). Multiple studies have demonstrated that a higher number of spinal lesions is associated with elevated levels of kappa light chain (8). This correlation suggests that spinal lesions contribute to the production or release of the kappa light chain, potentially indicating an underlying inflammatory process in the spinal cord. There was no correlation between the number of spinal lesions and the level of free kappa light chain in our study. However, further research is needed to establish a definitive causal relationship between the number of spinal lesions and kappa light chain levels in MS patients.

Table 1. Demographic parameters, laboratory data, and cerebrospinal fluid results

Variables	All population n=72
Gender, n (%)	
Female	51 (70.8)
Male	21(29.2)
Age, years	38.6±10.2
MS type, n (%)	
RRMS	52 (72.2)
PPMS	4 (5.6)
SPMS	10 (13.9)
CIS	1 (1.4)
RIS	5 (6.9)
OCB, n (%)	
Type 1	40 (55.6)
Type 2, 3	32 (44.4)
IgG	0.8 (0.4-2.8)
Spinal lession, n (%)	
No	31 (43.1)
Yes	41 (56.9)
EDSS	1 (0-6)
Free kappa-LC	15.2 (8.8-48.6)
Serum kappa-LC	2.8 (1.5-7.3)

RRMS: Relapsing-remitting MS, PPMS: Primary progressive MS, SPMS: Secondary progressive MS, CIS: Clinically isolated syndrome, OCB: Oligoclonal band, EDSS: Expanded Disability Status scale, IgG: Immunoglobulin G, MS: Multiple sclerosis

Table 2. The relationship between kappa-LC and clinical findings according to the presence and type of OCB

Variables	Free Kappa LC		Serum Kappa LC	
	r	p	r	p
OCB type 1				
IgG index	-0.5	0.667	-0.500	0.667
EDSS	0.122	0.467	-0.063	0.707
Number of lession	-0.059	0.725	0.053	0.753
Number of spinal lession	0.082	0.625	-0.119	0.476
OCB type 2, 3				
IgG index	0.114	0.556	0.013	0.946
EDSS	0.001	0.996	0.026	0.888
Number of lession	0.139	0.447	-0.084	0.647
Number of spinal lession	-0.248	0.172	0.074	0.686

OCB: Oligoclonal band, EDSS: Expanded Disability Status scale, IgG: Immunoglobulin G

In addition, other factors, such as the type of MS, disease duration, and treatment status, should be considered when interpreting the results.

Patients with increased kappa light chain have a higher risk of relapses and a poorer response to disease-modifying therapies, such as interferon-beta and glatiramer acetate (9). These findings highlight the importance of considering the type of OCBs when determining treatment strategies for MS patients. Because of the insufficient number of patients in the treatment class group in our study, no conclusive data on this issue could be obtained.

CONCLUSION

The relationship between the kappa light chain and clinical findings or cranial and spinal lesions in MS, particularly in the context of OCBs, is an emerging area of research. While the presence of OCBs in general suggests intrathecal IgG synthesis, understanding the specific role of the kappa light chain can provide additional insights into disease severity, clinical subtypes, and treatment response. Further investigations and prospective studies are required to unravel the underlying mechanisms and clinical implications associated with the kappa light chain. Such knowledge can contribute to personalized treatment approaches and improved prognosis for patients with MS.

ETHICS

Ethics Committee Approval: University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee approval was obtained using protocol number 2022/191 and decision number 2022-12-03 (date: 20.06.2022).

Informed Consent: Written consent was obtained from the legal caregivers of the patients.

Authorship Contributions

Surgical and Medical Practices: İ.A., Concept: V.Y., İ.A., E.D.D.P., Design: İ.A., Data Collection or Processing: A.M.Y., Y.Ç., A.G., Analysis or Interpretation: V.Y., İ.A., Literature Search: A.M.Y., Y.Ç., A.G., E.D.D.P., Writing: İ.A., A.M.Y., Y.Ç., A.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. JAMA 2021;325:765-79.
2. Deisenhammer F, Zetterberg H, Fitzner B, Zettl UK. The Cerebrospinal Fluid in Multiple Sclerosis. Front Immunol 2019;10:726.
3. Ferraro D, Trovati A, Bedin R, Natali P, Franciotta D, Santangelo M, et al. Cerebrospinal fluid kappa and lambda free light chains in oligoclonal band-negative patients with suspected multiple sclerosis. Eur J Neurol 2020;27:461-7.
4. Ben Noon G, Vigiser I, Shiner T, Kolb H, Karni A, Regev K. Reinforcing the evidence of oligoclonal bands as a prognostic factor in patients with Multiple sclerosis. Mult Scler Relat Disord 2021;56:103220.
5. Hegen H, Berek K, Bsteh G, Auer M, Altmann P, Di Pauli F, et al. Kappa free light chain and neurofilament light independently predict early multiple sclerosis disease activity-a cohort study. EBioMedicine 2023;91:104573.
6. Konen FF, Hannich MJ, Schwenkenbecher P, Grothe M, Gag K, Jendretzky KF, et al. Diagnostic Cerebrospinal Fluid Biomarker in Early and Late Onset Multiple Sclerosis. Biomedicines 2022;10:1629.
7. Moccia M, Ruggieri S, Ianniello A, Toosy A, Pozzilli C, Ciccarelli O. Advances in spinal cord imaging in multiple sclerosis. Ther Adv Neurol Disord 2019;12:1756286419840593.
8. Castillo-Villalba J, Gil-Perotín S, Gasque-Rubio R, Cubas-Nuñez L, Carratalà-Boscà S, Alcalá C, et al. High Levels of Cerebrospinal Fluid Kappa Free Light Chains Relate to IgM Intrathecal Synthesis and Might Have Prognostic Implications in Relapsing Multiple Sclerosis. Front Immunol 2022;13:827738.
9. Süße M, Konen FF, Schwenkenbecher P, Budde K, Nauck M, Grothe M, et al. Decreased Intrathecal Concentrations of Free Light Chains Kappa in Multiple Sclerosis Patients Taking Very High Effective Disease-Modifying Treatment. Diagnostics (Basel) 2022;12:720.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:287-295
DOI: 10.4274/BMJ.galenos.2023.2023.8-2

Research

Evaluation of Ventilator-associated Pneumonia Approaches in Pediatric Intensive Care Units in Türkiye

Türkiye'de Çocuk Yoğun Bakım Ünitelerinde Ventilatör İlişkili Pnömoni Yaklaşımlarının Değerlendirilmesi

Murat Tanyıldız[1], Furkan Yavuz[1], Karya Şenköylü[1], Ömer Özden[1], Dinçer Yıldızdaş[2]

[1]Koç University Faculty of Medicine, Department of Pediatric Intensive Care, İstanbul, Türkiye
[2]Çukurova University Faculty of Medicine, Department of Pediatric Intensive Care, Adana, Türkiye

ABSTRACT

Objective: The purpose of this study was to collect data on the management of ventilator-associated pneumonia (VAP) in pediatric intensive care units (PICU) in Türkiye and to determine the need for new national pediatric VAP guidelines.

Methods: In this multicenter cross-sectional study, an online questionnaire was disseminated via email to PICUs in various cities across Türkiye. One person at each PICU, namely, the clinician who made the treatment decisions, completed the questionnaire. The VAP diagnosis and treatment algorithms of the PICUs were analyzed using the data obtained from the questionnaires.

Results: Of the initial 32 PICUs, 30 units in 19 cities completed the questionnaire. The average number of beds in the units was 13.13±6.16, and the number of beds per nurse per shift was 2.13±0.57. The mean duration of mechanical ventilation was 5.8±4.2 days. The mean VAP frequency was 2.81% and the mean VAP rate was 5.04 per 1000 ventilator day. Distal airway culture sampling was performed in 86.7% of the units before antibiotic treatment was initiated. The most common agent was *Pseudomonas aeruginosa*, followed by *Klebsiella pneumonia* and *Acinetobacter baumannii*. When the resistance status of the isolates was analyzed, anti-pseudomonal penicillin resistance was 81.2%, anti-pseudomonal cephalosporin resistance was 84.5% for Pseudomonas aeruginosa; cefepime and ceftazidime resistance was 80.5% for *Klebsiella pneumonia*, and carbapenem resistance was 47.5% for *Acinetobacter baumannii*. A nurse-bed ratio >2 made a significant difference in the VAP rates between the PICUs ($p<0.05$).

Conclusion: Consensus exists regarding the need to reduce VAP in PICUs in Türkiye, and up-to-date national guidelines are essential to maximize the efficiency of PICUs.

Keywords: Ventilator-associated pneumonia, multi-center study, pediatric intensive care unit

ÖZ

Amaç: Bu çalışmanın amacı, Türkiye'de çocuk yoğun bakım ünitelerinde (ÇYBÜ) ventilatör ilişkili pnömoni (VİP) yönetimiyle ilgili uygulamalar hakkında veri toplamak ve yeni ulusal pediatrik VİP kılavuzuna olan ihtiyacı belirlemektir.

Gereç ve Yöntem: Bu çok merkezli kesitsel çalışmada, Türkiye'nin çeşitli illerindeki ÇYBÜ'lere e-posta yoluyla çevrimiçi bir anket gönderildi. Her ÇYBÜ'de tedavi kararını veren yalnızca bir klinisyen anketi doldurdu. Anketlerden elde edilen veriler kullanılarak ÇYBÜ'lerin VİP tanı ve tedavi algoritmaları analiz edildi.

Bulgular: On dokuz ilden toplam 32 ÇYBÜ çalışma davetini kabul etti, 30 merkez anketi eksiksiz tamamladı. Birimlerdeki ortalama yatak sayısı 13,13±6,16, vardiyada hemşire başına düşen hasta sayısı ise 2,13±0,57 idi. Ortalama mekanik ventilasyon süresi 5,8±4,2 gündü. Ortalama VİP sıklığı %2,81 ve ortalama VİP oranı 5,04/1000 ventilatör günü idi. Ünitelerin %86,7'sinde antibiyotik tedavisi başlanmadan önce distal hava yolu kültürü alındığı görüldü. En sık etken *Pseudomonas aeruginosa* idi, bunu *Klebsiella pneumonia* ve *Acinetobacter baumannii* izledi. İzolatların direnç durumları incelendiğinde, Pseudomonas aeruginosa'da antipsödomonal penisilin direnci %81,2, antipsödomonal sefalosporin direnci %84,5; *Klebsiella pneumonia* için sefepim ve seftazidim direnci %80,5, *Acinetobacter baumannii* için karbapenem direnci %47,5 olarak bulundu. Hemşire-yatak oranı >2 olması ÇYBÜ'ler arasında VİP oranlarının yükselmesi üzerinde çoklu değişken analizinde istatistiksel olarak anlamlı bir fark yarattı ($p<0,05$).

Address for Correspondence: Murat Tanyıldız, Koç University Faculty of Medicine, Department of Pediatric Intensive Care, İstanbul, Türkiye
Phone: +90 506 240 94 60 E-mail: mtanyildiz@kuh.ku.edu.tr ORCID ID: orcid.org/0000-0001-8804-032X

Cite as: Tanyıldız M, Yavuz F, Şenköylü K, Özden Ö, Yıldızdaş D. Evaluation of Ventilator-associated Pneumonia Approaches in Pediatric Intensive Care Units in Türkiye. Med J Bakirkoy 2023;19:287-295

Received: 07.08.2023
Accepted: 21.08.2023

Sonuç: Türkiye'deki ÇYBÜ'lerde VİP'nin azaltılması gerekliliği konusunda fikir birliği vardır ve ÇYBÜ'lerin etkinliğini en üst düzeye çıkarmak için ulusal güncel kılavuzlar ve uygulamalara ihtiyaç vardır.

Anahtar Kelimeler: Ventilatör ilişkili pnömoni, çok merkezli çalışma, çocuk yoğun bakım ünitesi

INTRODUCTION

Ventilator-associated pneumonia (VAP) is a nosocomial pneumonia that develops in pediatric intensive care unit (PICU) patients who receive a protocol based on mechanical ventilation (MV) for at least 48 hours (1). VAP is second in line after bloodstream-related infections and constitutes 20% of the extensive number of nosocomial infections encountered in PICUs (2). Although its incidence varies depending on the selected descriptive criteria, it affects 12% of children who receive MV (3). Despite its decreased incidence with the use of bundle applications, mortality in relation to VAP still varies between 20% and 50% by virtue of multidrug resistance (MDR) bacteria development (4). Apart from mortality, one of the most important challenges related to VAP is the prolongation of ICU stay, which directly influences hospitalization costs. It has been shown that VAP prolongs MV therapy by 10 days and the hospital stay by 12 days, and hospital costs are five times higher (5). The most important step in the fight against VAP is to take all necessary measures to reduce the risk factors and administer prompt and appropriate treatment (6). Therefore, VAP prevention and treatment guidelines, supported by current studies, have been established. One of the most important guidelines is that published by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS), the IDSA/ATS guidelines, in 2016 (7). Additionally, under the leadership of the European Respiratory Society (ERS), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the European Society of Intensive Care Medicine (ESICM), and the Latin American Thoracic Societies (ALAT), the ERS/ESICM/ESCMID/ALAT guidelines were developed in 2017 (1). Although there are numerous similarities in the approaches between the two sets of guidelines, some important points can make considerable differences. Both guidelines are designed for adults and are applied to pediatric patients, which has resulted in ambiguous views on current VAP recommendations and their application. In Türkiye, the national pediatric guidelines issued by the Turkish Thoracic Society (TTS) in 2009 under the name "Consensus Report on the Diagnosis and Treatment of Hospital-Developing Pneumonia in Children" have not been updated for more than 10 years (8). Over the past decade, pan-resistant bacteria have developed, which has introduced a new generation of antibiotics to combat these agents. In addition, new concepts have emerged, such as the implementation of inhaled antibiotics and the diagnosis of ventilator-associated tracheobronchitis (VAT) and ventilator-associated events. This period has also seen a rapid increase in the number of centers and PICUs that provide fellowship education programs in Türkiye. Considering these developments, we believe that acknowledging the changes in VAP practices over the past 10 years may open many doors to improving tertiary care services in Türkiye. The aim of this study was to collect data on procedures related to VAP in Turkish PICUs and to assess the need for new national pediatric guidelines. Our study has the unique feature of being the first study on VAP conducted in PICUs in Türkiye, and 30 units from around the country participated.

METHODS

This multicenter descriptive, cross-sectional, and quantitative study was conducted after obtaining approval from the Koç University Institutional Ethics Committee (decision no: 2021.372.IRB2.071, date: 07.10.2021). An online 35-item questionnaire (Qualtrics Survey System, https://koc.ca1.qualtrics.com/jfe/form/SV_9MqUd0i5dig3f6e) was sent directly to PICUs via email, and only the person from each unit who made treatment decisions was allowed to fill in the questionnaire. Only the PICUs that completed the questionnaire were included in the study. After the first email, three reminder emails were sent to the units at one-week intervals. Informed consent was obtained from each unit before responding to the questionnaire. Using the data obtained from the questionnaire, the VAP diagnosis and treatment approaches of the units were analyzed and reported.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences for Windows version 23.0. The number, percentage, mean, standard deviation, and median were used as descriptive statistics to evaluate the data. A chi-square test was used to compare the categorical variables, and multivariate logistic regression was performed to assess the factors related to higher VAP rates. A p-value <0.05 was considered statistically significant.

RESULTS

We invited 38 PICUs from across Türkiye to participate in this study. Of the 32 units that provided their consent, 30 PICUs from 19 cities completed the questionnaire. Among them, 60% (n=18) were PICUs in university-affiliated hospitals, whereas 40% (n=12) were units in Ministry of Health-affiliated hospitals (Figure 1). All the participating units were third-level mixed ICUs with both medical and surgical patients, and 50% of them provided care for postoperative cardiac patients. The average number of beds in the units was 13.13±6.16 [median 14 (5-32)], and the mean number of nurses was 25.63±13.48 [median =23.5 (10-66)]. The number of beds per nurse per shift was 2.13±0.57. The average number of patients followed per year was 200-400 in 33.3% of the units, 400-600 in 26.7%, and 600-800 in 30%. The corresponding number of patients on MVs followed annually was 50-100 patients in 26.7% of the units, 101-200 patients in 16.7%, 201-300 patients in 30%, and 301-400 patients in 23.3%. The mean duration of MV was 5.8±4.2 days, with 53.3% of PICUs applying MV for between 1 and 7 days (Table 1). In terms of defining VAP, only 26.7% of the PICUs used the IDSA/ATS definition, and the remaining 73.3% used the definition of the Center for Disease Control and Prevention. The mean VAP frequency was 2.81% and the mean VAP rate was 5.04 per 1000 ventilator day. The VAP frequency was between 0% and 5% in 76.67% of the PICUs, and the VAP rate was between 0 and 5 per 1000 ventilator days in 73.3% of the units (Figure 2). *Pseudomonas aeruginosa* (*P. aeruginosa*) was the most common agent (43.3% of cases), followed by *Klebsiella pneumoniae* (*K. pneumoniae*) (33.3%) and *Acinetobacter baumannii* (*A. baumannii)* (16.7%) (Table 2). When the resistance status of the isolates was analyzed, anti-pseudomonal penicillin resistance was 81.2%, anti-pseudomonal cephalosporin resistance was 84.5% for *P. aeruginosa*; cefepime–ceftazidime resistance was 80.5% for *K. pneumoniae*, and carbapenem resistance was 47.5% for *A. baumannii.* Regarding VAP protection, bundle applications were used in all the units, with an average of 14.2±5.6 of the applications listed in Table 3 implemented at each PICU. Before starting antibiotic treatment, 86.7% of the PICUs conducted distal airway culture sampling. Among them, 66.7% of the units used only the non-invasive semiquantitative technique of endotracheal aspiration (ETA) and never used the invasive quantitative culture method of bronchoalveolar lavage (BAL). Of these units, 20% used ETA first, before sending a BAL sample in patients who were unresponsive to treatment. Another 3.3% of the PICUs only used the BAL technique for diagnoses, whereas 6.7% started antibiotic treatment directly without sending any culture samples for analysis. Of the units, 86.6% performed de-escalation after starting antibiotics, and among them, 73.3% obtained cultures and started antibiotics and de-escalated based on the clinical and culture results. Meanwhile, 13.3% obtained cultures only and began antibiotic treatment after 2-3 days, with de-escalation according to the clinical, culture,

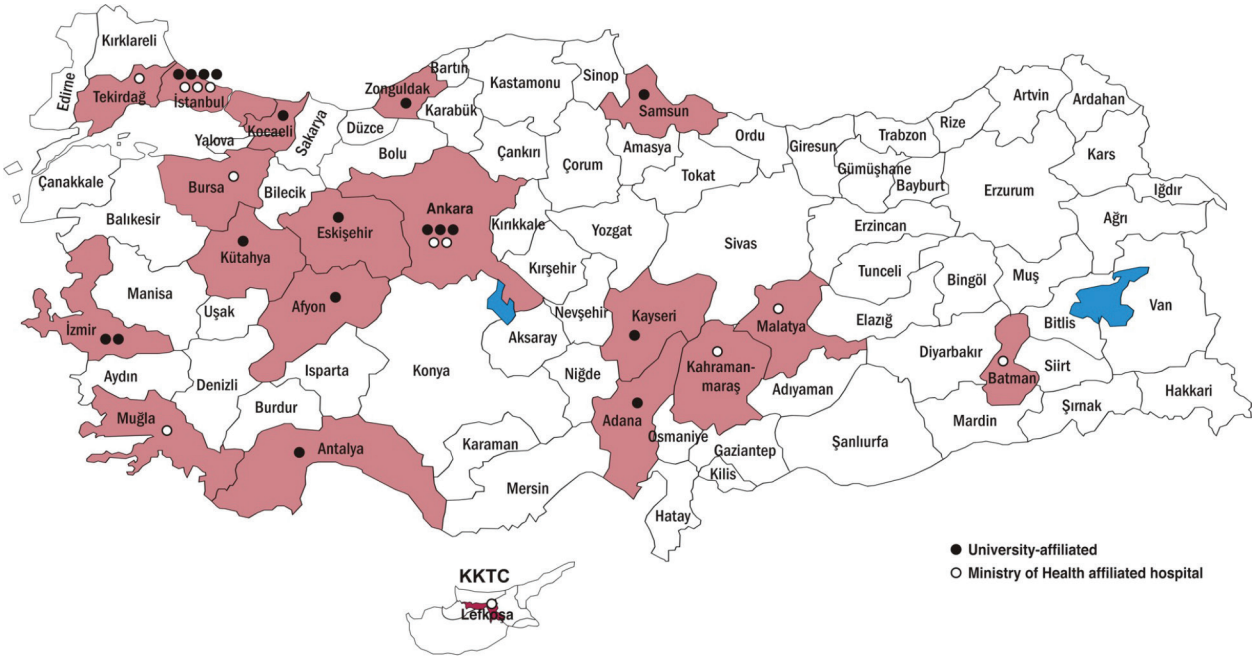

Figure 1. Pediatric intensive care units participating the study in Türkiye

Table 1. General features of pediatric intensive care units

Unit (n=30)	Unit number (n) mean	%
University affiliated	18	60
Ministry of Health affiliated	12	40
Properties of PICU		
Medical + surgical	16	53
Medical + surgical + cardiac	14	47
Number of beds (mean)	13.13±6.16	
Ratio of nurse to bed (mean)	2.13±0.57	
Annual patient range in PICUs		
200-400	10	33.3
400-600	8	26.7
600-800	9	30.0
800-1000	1	3.3
>1000	2	6.7
Annual interval of patient in MV		
0-100	8	26.7
101-200	5	16.7
201-300	9	30.0
301-400	7	23.3
>400	1	3.3
MV duration range in PICUs		
1-7 days	16	53.3
8-10 days	10	33.3
11-14 days	4	13.3

MV: Mechanical ventilation, PICU: Pediatric intensive care unit

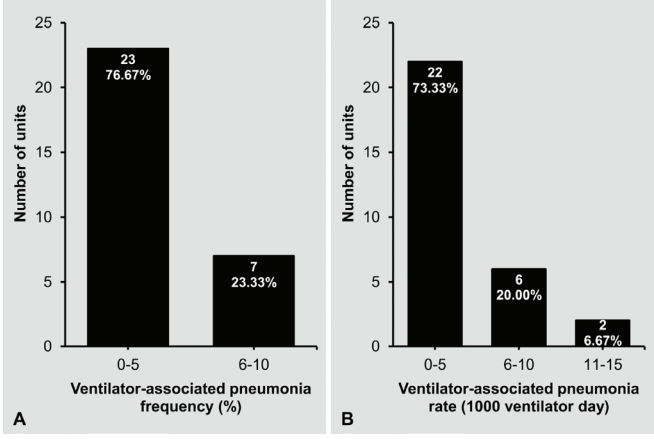

Figure 2. The ventilator-associated pneumonia (VAP) frequency and rates in pediatric intensive care units (PICU) A) The VAP frequency was between 0% and 5% in 76.67% of the PICUs B) the VAP rate was between 0-5 per 1000 ventilator days in 73.3% of the PICUs

and procalcitonin (PCT) results. A few PICUs (6.7%) took cultures and started antibiotics but were not de-escalate. Considering the general duration of antibiotic use for treating VAP (excluding patients with cavitation, necrotizing pneumonia, abscess, and empyema), 23.3% of the PICUs applied treatment against non-resistant Gram-negative bacteria for 7 days and terminated the treatment based on the PCT results. More than half (56.7%) of the units provided 14-day therapy for non-resistant Gram-negative bacteria and terminated the treatment in line with the PCT results. Regardless of the duration, 10% of the units used antibiotics until both a clinical and radiological recovery was achieved, and this treatment was discontinued based on the PCT response. In terms of VAT treatment approaches, 43.3% of the PICUs observed the patients without starting antibiotic treatment, 23.3% started antibiotics immediately, and 33.3% did not start antibiotics but instead followed the clinical and acute phase response. With respect to inhaled antibiotics, 56.7% of the PICUs did not use them, 16.7% used them in patients with VAP with carbapenem-resistant and colistin-sensitive *Acinetobacter* growth, and

Table 2. Microorganism profile of ventilator-associated pneumonia in PICUs in Türkiye

Unit (n=30)	Units (n)	Percent (%)
1st most common VAP agent in PICU		
Pseudomonas aeruginosa	13	43.3
Klebsiella pneumoniae	10	33.3
Acinetobacter baumannii	5	16.7
Stenotrophomonas maltophilia	1	3.3
Staphylococcus aureus	1	3.3
2nd most common VAP agent in PICU		
Klebsiella pneumoniae	15	50.0
Acinetobacter baumannii	9	30.0
Stenotrophomonas maltophilia	3	10.0
Pseudomonas aeruginosa	3	10.0
3rd most common VAP agent in PICU		
Acinetobacter baumannii	11	36.7
Pseudomonas aeruginosa	7	23.3
Klebsiella pneumoniae	5	16.7
Staphylococcus aureus	3	10.0
Stenotrophomonas maltophilia	2	6.7
Enterobacteriaceae	1	3.3
Candida spp.	1	3.3

PICU: Pediatric intensive care unit, VAP: Ventilator-associated pneumonia

Table 3. Bundle component for prevention of ventilator-associated pneumonia

Adherence to hand-hygiene guidelines.
Avoid the use of broad-spectrum and long-term parenteral antibiotic.
Elevation of the head of the bed 30-45° (semi recumbent position).
Regular oral hygiene care methods are applied according to the age of the patient.
Only cuffed tube and orotracheal way preferred for entubation and tube placement is checked frequently to prevent self-extubation.
Non-invasive ventilation offered whenever possible and avoid prolonged mechanical ventilation.
Re-entubation should be prevented. Improve planned extubation with the design of protocols to improve quality.
Unnecessary patient transport is not acceptable.
Endotracheal cuff pressure is routinely checked and maintained between 15-20 mmHg.
Subglottic aspiration yield precedence to oral aspiration.
Ventilator circuit replacement and circuit manipulation are limited. Circuit changes only when visibly soiled or malfunctioning.
Deep sedation is avoided, sedation interruption and spontaneous breathing trials is provided.
Unnecessary peptic ulcer protection [proton pumb inhibitors and histamin receptor 2 (H2) antagonist] are not used.
Disposable one use sterile water is used for in-tube aspiration, avoid saline lavage with suctioning.
Prevent gastric over distention.
Education of the healthcare workers regarding nasocomial infection and VAP prevention.
Deep vein thrombosis prophylaxis is used.

VAP: Ventilator-associated pneumonia

13.3% used them for patients with VAP with carbapenem-resistant, colistin-susceptible all Gram-negative bacteria growth. In our questionnaire, we enquired about the approach toward acute phase reactant responses in the routine practices of the PICUs and found that 43.3% of the units used the acute phase reactant levels at the time of diagnosis, when evaluating the treatment response, and when deciding whether to discontinue treatment. Furthermore, 33.3% of the units used these at both the time of diagnosis and the evaluation of the 72-hour treatment response, 13.3% followed the acute phase reactant levels at the time of diagnosis and daily, whereas 6.7% applied them in their practice only at the time of diagnosis. When the VAP protocols used by the PICUs were queried, 26.7% of the units indicated that they used their own protocols, 26.7% used the IDSA/ATS guidelines, 3.3% used the ERS/ESCMID/ALAT guidelines, and 10% used the TTS national guidelines. In contrast, 33.3% did not use any VAP protocols. When factors such as patient profile (medical + surgery versus medical + surgery + cardiac), nurse-to-bed ratio, MV time, bundle application, culture method, antibiotic duration, and the VAP protocol used by the PICUs were compared between the units with a VAP rate of >5 to ≤5 per 1000 ventilator days, only having a nurse-patient ratio >2 made a significant difference to the VAP ratio between the units [odds ratio (OR), 1.22; 95% confidence interval (CI), 1.15-1.28; p<0.01].

DISCUSSION

Our study included 30 tertiary-level PICUs in Türkiye that had completed our online questionnaire (Figure 1). Although the distribution of the units included in the study was not homogeneous across the country (19 cities), the inclusion of the provinces with the highest populations and patient densities was very important when evaluating the general situation in Türkiye. When the average number of patients followed up in the PICUs per year was examined, we observed that most of the units had a very intensive patient follow-up schedule of over 400 patients per year. Accordingly, the number of patients receiving MV treatment exceeded 200 per year in most of the units. When the VAP frequency and VAP rates of the units were evaluated, the mean VAP frequency was 2.81% and the VAP rate was 5.04 per 1000 ventilator days. The International Nasocomial Infection Control Consortium (INICC) study was conducted in 36 countries between 2004 and 2009, and the results showed that the average VAP frequency observed in the 45 PICUs participating in the study was 2.5%, with a VAP rate of 6.5 per 1000 ventilator days (9). In recent prospective studies conducted in PICUs, the VAP rate was found to vary between 5.4 and 41 per 1000 ventilator days (10-12). In a study conducted in a cardiac ICU where only postoperative pediatric cardiac patients were followed up, the VAP rate was 29 per 1000 ventilator days, which was considerably higher than the general average VAP rate seen in PICUs (13). In our study, no significant difference was found in the VAP rate between the PICUs where postoperative cardiac patients were followed up and those where such patients were not. With the widespread introduction of bundle measures in PICUs, a significant decrease in VAP rates has been observed. Kunzman et al. (14) showed that the VAP rate decreased from 55 to 19 per 1000 ventilator days in 5 months with five bundle practices, namely, 1) 30° head elevation, 2) age-appropriate oral care, 3) inspection of the location of the oro/nasogastric tubes every 3-4 hours by marking them with a marker after the location of the

tubes was confirmed, 4) avoiding the routine use of saline before endotracheal tube aspiration, and 5) positioning the set to prevent water accumulation in the ventilator set and directing water to the water trap reservoir. In the same study, when a coordinator supervised these practices and provided one-to-one training, the VAP rate decreased to 4 per 1000 ventilator days (14). The use of the INICC Multidimensional Approach and INICC Surveillance Online System applications, i.e., 1) bundle applications, 2) training, 3) outcome surveillance, 4) process surveillance, 5) VAP rate feedback, and 6) performance feedback, led to a decrease in the VAP rate from 7.84 to 4.74 per 1000 ventilator days (15). In our study, we observed that bundle practices were performed in all PICUs. An average of 14.2±5.6 measures from the bundle practices (Table 3) were implemented, and compliance with the bundle practices was supervised by the respective infection control committees and coordinators. All PICUs demonstrated the following common practices: 1) adherence to hand hygiene; 2) avoidance of the use of long-term and broad-spectrum antibiotics; 3) bed head-level elevation by 30°-45°; 4) age-appropriate oral hygiene; 5) preference for only a cuffed tube and the orotracheal method for intubation, and the oro/nasogastric tube was checked frequently; and 6) preference for non-invasive ventilation whenever possible with an avoidance of prolonged MV.

One of the most important ways to decrease the VAP rate is to shorten the duration of MV and the length of ICU stay. In a recent study, Rosenthal et al. (16) showed that a longer length of ICU stay, which increased the VAP risk by 7% per day (OR, 1.07; 95% CI, 1.07-1.08; $p<0.0001$), and longer MV duration (OR, 0.96; 95% CI, 0.95-0.96; $p<0.0001$) were independent risk factors for VAP. In a single-center study, Chompton et al. (12) showed that patients with VAP had a longer MV duration and ICU stay than those without VAP (15 days vs. 6 days, and 19 days vs. 9 days, respectively). In our study, the mean duration of MV was 5.8±4.2 days, which supports the rate of VAP found in our study. However, when the PICUs with VAP rates below and above 5 per 1000 ventilator days were compared, no significant difference was found in terms of MV duration (MV, <7 vs. >7 days, respectively). We performed a multivariate logistic regression analysis to determine the factors affecting VAP incidence; the nurse-patient ratio was found to be significantly related. When we compared the units with VAP rates below 5 per 1000 ventilator days with the units with VAP rates above 5 per 1000 ventilator days, a nurse-patient ratio >2 significantly increased the VAP rate ($p<0.05$). A recent study showed that the incidence of VAP was closely related to nursing services, especially the number of patients per nurse during night shifts, and the level of experience of the nurses directly affected the incidence of VAP (17).

When we examined the frequency ranking of the VAP agents seen in the PICUs in our study, we observed that *P. aeruginosa* had the highest ranking, followed by *K. pneumoniae* and *A. baumannii*. All three types showed resistance to at least two drugs. VAP caused by MDR Gram-negative bacteria is a major global problem. In studies conducted in Europe and the USA on VAP, it was observed that the prevalence of Gram-negative bacteria had increased to 76.13%-95.3% since 2010, and *P. aeruginosa* and *A. baumannii* were the leading agents (18-20). In the USA, carbapenem resistance in *P. aeruginosa* has been shown to reach 16.1%-28.4%, resistance to anti-pseudomonal penicillins (piperacillin-tazobactam) 15.6%-19.1%, and resistance to anti-pseudomonal cephalosporins (e.g., ceftazidime or cefepime) 9.5%-29.4%, and these figures are gradually increasing. While colistin resistance in *P. aeruginosa* is approximately 2% in the USA, resistance is increasing in Europe and the Mediterranean region (21). In our study, anti-pseudomonal penicillin resistance and anti-pseudomonal cephalosporin resistance were found in >80% of the patients with *P. aeruginosa*, 80.5% of those with *K. pneumonia*, and 47.5% of the patients with *A. baumannii*, which indicates a serious issue in PICUs in Türkiye.

Both the IDSA/ATS and ERS/ESICM/ESCMID/ALAT guidelines recommend distal airway sampling and cultures before providing treatment, whereas the IDSA/ATS guidelines recommend a non-invasive semiquantitative ETA culture method. In meta-analyses and Cochrane data, it has been shown that the culture technique does not change clinical outcomes, such as mortality, length of ICU stay, and mean MV duration (22). In general, semiquantitative ETA cultures have a higher sensitivity and lower specificity (23). However, because no evidence has been provided to show that invasive quantitative cultures will lead to better clinical outcomes, non-invasive semiquantitative cultures are recommended because non-invasive sampling is easier and faster and causes fewer complications (7). The ERS/ESICM/ESCMID/ALAT guidelines recommend that invasive quantitative (BAL, mini-BAL) methods should be used in stable patients, if possible, when taking cultures. However, due to problems such as the increased oxygen requirements of patients during this method and the risks associated with the procedure, such as bleeding, bronchospasm, and technical impossibilities, this recommendation is considered to have low evidence value and has been classified as a weak

recommendation because of insufficient supporting data. The mini-BAL application has also been recommended as an alternative to the BAL application because it is a less invasive technique (1). In our study, the majority of PICUs used non-invasive semiquantitative methods (in line with the IDSA/ATS guidelines), as invasive methods are more difficult to apply in the pediatric age group.

A diagnosis of VAP should be made very rapidly. Inappropriate and late initiation of antibiotic therapy significantly increases the risk of morbidity and mortality in patients with VAP. The diagnosis is based on radiological and clinical findings. The Clinical Pulmonary Infection score, C-reactive protein (CRP), and PCT are not included in the IDSA/ATS or ERS/ESICM/ESCMID/ALAT guidelines for the diagnosis of VAP and antibiotic initiation. The IDSA/ATS guidelines strongly discourage the use of biomarkers, CRP, and PCT at the time of diagnosis and emphasize that daily serial CRP and PCT monitoring is a highly unnecessary and cost-increasing practice. In our study, we found that most PICUs performed CRP and PCT control at diagnosis, evaluated the treatment response, and discontinued treatment, which is not recommended in the guidelines. Performed daily serial CRP and PCT monitoring, which is undoubtedly a remarkable finding in terms of practice, as it may increase both the cost and duration of antibiotic use.

The IDSA/ATS and ERS/ESICM/ESCMID/ALAT guidelines agree that 7-8 days of antibiotic treatment is sufficient for VAP (1,7). However, the ERS/ESICM/ESCMID/ALAT guidelines also emphasize that treatment should be tailored to the patient, and longer antibiotic use may be required in patients with immunodeficiency, cystic fibrosis, empyema, lung abscess, cavitation, or necrotizing pneumonia and in those in whom inappropriate treatment was previously started (1). In our study, when the duration of antibiotic use in VAP in the absence of immunodeficiency, cystic fibrosis, empyema, lung abscess, cavitation, and necrotizing pneumonia was examined, we found that most of the PICUs (56.7%) preferred long-term (14 days') treatment, and 23.3% discontinued treatment if PCT was negative after 7 days (short-term) treatment.

De-escalation is recommended in many international and national guidelines to prevent the high costs, side effects, and possible development of resistance that may be caused by the overuse of antibiotics. When studies on the subject were examined, it was noted that most of the studies were observational studies, randomized controlled studies were few in number, the studies were not blinded, and they had a high risk of bias (7,24). Moreover, no difference was found between the de-escalation and continuous antibiotic treatment groups in terms of mortality and duration of ICU stay. However, when all these studies and clinical observations were evaluated together, the beneficial aspects of the de-escalation approach in VAP outweighed the risks, and de-escalation has thus been recommended in both the IDSA/ATS and ERS/ESICM/ESCMID/ALAT guidelines (1,7). When the de-escalation approach of the PICUs in our study was evaluated, we observed that 73.3% of cases were de-escalated based on culture growth.

In studies and meta-analyses on the use of inhaled antibiotic therapy for treating VAP, inhaled antibiotics used in addition to systemic antibiotic therapy, especially in VAP caused by gram-negative bacteria with MDR characteristics, were found to increase the rate of recovery and shorten the duration of intravenous antibiotic use and MV time (7,25,26). The IDSA/ATS guidelines recommend the use of inhaled antibiotics in addition to systemic treatment in VAP caused by Gram-negative bacilli susceptible only to aminoglycosides or polymyxin (colistin or polymyxin B) because it shortens the duration of intravenous antibiotic use and recovery time and reduces costs (7). In our study, the majority of PICUs did not use inhaled antibiotics; however, considering the high incidence of carbapenem-resistant, colistin-sensitive *A. baumannii*, the use of inhaler antibiotics should be included in the national VAP guidelines.

The most important limitation of our study was that the data were obtained via a questionnaire. However, to increase the reliability of the data, only one person, namely, the person who made the treatment decision (department director or assistant director), from each PICU completed the questionnaire.

CONCLUSION

We found a general consensus on the diagnosis, treatment, and prevention of VAP in PICUs in Türkiye. Furthermore, there has been considerable rational progress in the fight against VAP. However, there is a need for updated national guidelines given the differences in international guidelines. The study's findings were critical in determining where a developing country stood in terms of addressing VAP in PICUs in accordance with current guidelines.

Acknowledgements

The authors gratefully acknowledge the statistical assistance of Canser Boz, Phd from İstanbul University, Faculty of Health Science. This study conducted with the collaboration of the members of "Ventilator-Associated Pneumonia in Pediatric Intensive Care Units in Türkiye (VAPPICT) Study

Group". VAPPICT Study Group: Gazi Aslan, Yasemin Çoban, Muhammed Üdürgücü, Nagehan Aslan, Mehmet Çeleğen, Serkan Özsoylu, Faruk Ekinci, Zeynel Abidin Ozturk, Mutlu Uysal Yazici, Tahir Dalkıran, Hakan Tekguc, Ayhan Yaman, Eylem Kıral, Serhat Emeksiz, Esra Şevketoğlu, Demet Demirkol, Tanıl Kendirli, Muhterem Duyu, Pınar Yazıcı Özkaya, Nurettin Onur Kutlu, Alper Köker, Oğuz Dursun, Sinan Yavuz, Feyza İncekoy Girgin, Ayşe Filiz Yetimakman, İbrahim Ethem Pişkin, Özlem Sarıtaş Nakip, Arzu Oto, Başak Yıldız, Ahmet Yöntem, Selman Kesici.

ETHICS

Ethics Committee Approval: This multicenter descriptive, cross-sectional, and quantitative study was conducted after obtaining approval from the Koç University Institutional Ethics Committee (decision no: 2021.372.IRB2.071).

Informed Consent: Informed consent was obtained from each participant before responding to the questionnaire.

Authorship Contributions

Concept: M.T., F.Y., D.Y., Design: M.T., F.Y., Data Collection or Processing: M.T., F.Y., K.Ş., Ö.Ö., D.Y., Analysis or Interpretation: M.T., F.Y., Ö.Ö., D.Y., Literature Search: M.T., K.Ş., Ö.Ö., Writing: M.T., F.Y., K.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J 2017;50:1700582.
2. Foglia E, Meier MD, Elward A. Ventilator-associated pneumonia in neonatal and pediatric intensive care unit patients. Clin Microbiol Rev 2007;20:409-25.
3. Chang I, Schibler A. Ventilator Associated Pneumonia in Children. Paediatr Respir Rev 2016;20:10-6.
4. Metersky ML, Wang Y, Klompas M, Eckenrode S, Bakullari A, Eldridge N. Trend in Ventilator-Associated Pneumonia Rates Between 2005 and 2013. JAMA 2016;316:2427-9.
5. Karaoglan H, Yalcin AN, Cengiz M, Ramazanoglu A, Ogunc D, Hakan R, et al. Cost analysis of ventilator-associated pneumonia in Turkish medical-surgical intensive care units. Infez Med 2010;18:248-55.
6. Martin-Loeches I, Torres A, Rinaudo M, Terraneo S, de Rosa F, Ramirez P, et al. Resistance patterns and outcomes in intensive care unit (ICU)-acquired pneumonia. Validation of European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) classification of multidrug resistant organisms. J Infect 2015;70:213-22.
7. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63:e61-111. Erratum in: Clin Infect Dis 2017;64:1298. Erratum in: Clin Infect Dis 2017;65:1435. Erratum in: Clin Infect Dis 2017;65:2161.
8. Demir E, Kara A, Ince E, Kiper N, Kuyucu N, Karabocuoglu M, et al. Turk Toraks Dernegi cocuklarda hastanede gelisen pnomoni tanı ve tedavi uzlaşı raporu. Thorac Res Pract 2009;10: Supplement 3-16.
9. Rosenthal VD, Bijie H, Maki DG, Mehta Y, Apisarnthanarak A, Medeiros EA, et al. International Nosocomial Infection Control Consortium (INICC) report, data summary of 36 countries, for 2004-2009. Am J Infect Control 2012;40:396-407.
10. van Wyk L, Applegate JT, Salie S. Ventilator-associated pneumonia in PICU - how are we doing? South Afr J Crit Care 2022;38:10.7196/SAJCC.2022.v38i2.536.
11. Vijay G, Mandal A, Sankar J, Kapil A, Lodha R, Kabra SK. Ventilator Associated Pneumonia in Pediatric Intensive Care Unit: Incidence, Risk Factors and Etiological Agents. Indian J Pediatr 2018;85:861-6.
12. Chomton M, Brossier D, Sauthier M, Vallières E, Dubois J, Emeriaud G, et al. Ventilator-Associated Pneumonia and Events in Pediatric Intensive Care: A Single Center Study. Pediatr Crit Care Med 2018;19:1106-13.
13. Shaath GA, Jijeh A, Faruqui F, Bullard L, Mehmood A, Kabbani MS. Ventilator-associated pneumonia in children after cardiac surgery. Pediatr Cardiol 2014;35:627-31.
14. Kunzmann H, Dimitriades K, Morrow B, Argent A. Reducing paediatric ventilator-associated pneumonia – a South African challenge! South Afr Crit Care 2016;32:17-20.
15. Al-Abdely HM, Khidir Mohammed Y, Rosenthal VD, Orellano PW, ALazhary M, Kaid E, et al. Impact of the International Nosocomial Infection Control Consortium (INICC)'s multidimensional approach on rates of ventilator-associated pneumonia in intensive care units in 22 hospitals of 14 cities of the Kingdom of Saudi Arabia. J Infect Public Health 2018;11:677-84.
16. Rosenthal VD, Jin Z, Memish ZA, Rodrigues C, Myatra SN, Kharbanda M, et al. Multinational prospective cohort study of rates and risk factors for ventilator-associated pneumonia over 24 years in 42 countries of Asia, Africa, Eastern Europe, Latin America, and the Middle East: Findings of the International Nosocomial Infection Control Consortium (INICC). Antimicrob Steward Healthc Epidemiol 2023;3:e6.
17. Yin Y, Sun M, Li Z, Bu J, Chen Y, Zhang K, et al. Exploring the Nursing Factors Related to Ventilator-Associated Pneumonia in the Intensive Care Unit. Front Public Health 2022;10:715566.
18. Assefa M. Multi-drug resistant gram-negative bacterial pneumonia: etiology, risk factors, and drug resistance patterns. Pneumonia (Nathan) 2022;14:4.
19. Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009-2012. Int J Antimicrob Agents 2014;43:328-34.
20. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, et al. Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol 2016;37:1288-301.
21. Rhodes NJ, Cruce CE, O'Donnell JN, Wunderink RG, Hauser AR. Resistance Trends and Treatment Options in Gram-Negative Ventilator-Associated Pneumonia. Curr Infect Dis Rep 2018;20:3.
22. Berton DC, Kalil AC, Teixeira PJ. Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia. Cochrane Database Syst Rev 2014:CD006482.

23. Solé Violán J, Fernández JA, Benítez AB, Cardeñosa Cendrero JA, Rodríguez de Castro F. Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia. Crit Care Med 2000;28:2737-41.
24. Khan RA, Aziz Z. A retrospective study of antibiotic de-escalation in patients with ventilator-associated pneumonia in Malaysia. Int J Clin Pharm 2017;39:906-12.
25. Tumbarello M, De Pascale G, Trecarichi EM, De Martino S, Bello G, Maviglia R, et al. Effect of aerosolized colistin as adjunctive treatment on the outcomes of microbiologically documented ventilator-associated pneumonia caused by colistin-only susceptible gram-negative bacteria. Chest 2013;144:1768-75.
26. Doshi NM, Cook CH, Mount KL, Stawicki SP, Frazee EN, Personett HA, et al. Adjunctive aerosolized colistin for multi-drug resistant gram-negative pneumonia in the critically ill: a retrospective study. BMC Anesthesiol 2013;13:45.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:296-301
DOI: 10.4274/BMJ.galenos.2023.2023.8-6

Research

Evaluation of Adult Patients with Childhood-onset Chronic Disease Admitted to the Intensive Care Unit

Yoğun Bakım Ünitesine Başvuran Çocukluk Çağı Başlangıçlı Kronik Hastalığı Olan Erişkin Hastaların Değerlendirilmesi

Gülbahar Çalışkan[1], Ayça Sayan[1], Halil Erkan Sayan[2], Nermin Kelebek Girgin[1]

[1]University of Health Sciences Türkiye, Bursa City Hospital, Clinic of Anesthesiology and Reanimation, Intensive Care Unit, Bursa, Türkiye
[2]University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Intensive Care Unit, Bursa, Türkiye

ABSTRACT

Objective: Many patients with childhood-onset chronic disease (CCD) can reach adulthood with improvements in medical treatments. They may require intensive care unit (ICU) admission for various reasons throughout their lives. The aim of this study was to evaluate the reasons for hospitalization and treatment processes of patients with CCD in the adult ICU.

Methods: The files of 69 patients with CCD who were treated in the adult ICU between June 1, 2010 and May 31, 2020 were retrospectively evaluated. Demographic characteristics, CCD and coexisting diseases, ICU admission diagnosis, treatment processes, and results were recorded.

Results: The patients were median age 24 (21-30.5) years 43.5% of whom were female. The most common CCD, comorbid disease, and diagnosis of ICU admission were cerebral palsy (27.5%), epilepsy (23.2%), and pneumonia (40.6%), respectively. Ten (52.6%) of 19 patients who died were lost due to sepsis. Mortality rates were significantly higher in patients with comorbid diseases, such as chronic lung disease or mental retardation ($p<0.005$).

Conclusion: We believe that the life expectancy of patients with childhood chronic illnesses is increasing, necessitating the development of adult ICUs to cater to these patients. Furthermore, it is essential to provide training to doctors and nurses working in ICUs for special patient care.

Keywords: Chronic childhood disease, cerebral palsy, intensive care

ÖZ

Amaç: Çocukluk çağında başlayan kronik hastalığı (ÇKH) olan birçok hasta, tıbbi tedavilerdeki gelişmelerle yetişkinliğe ulaşabilmektedir. Bu hastaların yaşamları boyunca çeşitli nedenlerle yoğun bakım ünitesine (YBÜ) yatışları gerekebilmektedir. Çalışmamızın amacı, erişkin YBÜ'lerde çocukluk çağında başlayan kronik hastalığı olan hastaların yatış nedenlerini ve tedavi süreçlerini değerlendirmekti.

Gereç ve Yöntem: 1 Haziran 2010 ve 31 Mayıs 2020 tarihleri arasında erişkin YBÜ'lerde tedavi edilen, ÇKH olan 69 hastanın dosyaları retrospektif olarak değerlendirildi. Demografik özellikler, ÇKH ile eşlik eden sistemik hastalıkları, YBÜ'ye yatış tanıları, tedavi süreçleri ve sonuçları kaydedildi.

Bulgular: Hastalar ortanca 24 (21-30,5) yaşındaydı ve %43,5'i kadındı. En sık görülen ÇKH, eşlik eden sistemik hastalık ve YBÜ'ye yatış tanısı sırasıyla serebral palsi (%27,5), epilepsi (%23,2) ve pnömoni (%40,6) idi. Ölen 19 hastanın 10'u (%52,6) sepsis nedeniyle kaybedilmişti. Kronik akciğer hastalığı veya mental retardasyon gibi yandaş hastalığı olanlarda ölüm oranları anlamlı olarak daha yüksekti ($p<0,005$).

Sonuç: ÇKH olan hastaların ortalama yaşam sürelerinin uzamakta olduğunu ve bu hastalara yönelik yetişkin YBÜ'lerin hazırlanması gerektiğini düşünmekteyiz. Ayrıca YBÜ'lerde çalışan doktor ve hemşirelere özellikli hasta bakımı için eğitim verilmesi gereklidir.

Anahtar Kelimeler: Çocukluk çağı kronik hastalıkları, serebral palsi, yoğun bakım

Address for Correspondence: Gülbahar Çalışkan, University of Health Sciences Türkiye, Bursa City Hospital, Clinic of Anesthesiology and Reanimation, Intensive Care Unit, Bursa, Türkiye
Phone: +90 224 975 26 08 E-mail: alkanbahar@yahoo.com ORCID ID: orcid.org/0000-0002-0053-9087

Cite as: Çalışkan G, Sayan A, Sayan HE, Kelebek Girgin N. Evaluation of Adult Patients with Childhood-onset Chronic Disease Admitted to the Intensive Care Unit. Med J Bakirkoy 2023;19:296-301

Received: 17.08.2023
Accepted: 26.08.2023

INTRODUCTION

Today, many patients with chronic diseases, such as congenital heart disease, cystic fibrosis, and cerebral palsy (CP), starting in childhood can reach adulthood with improvements in medical treatments (1-5). These patients, who are treated in pediatric intensive care units (ICUs) during the growing period, may require ICU hospitalization for various reasons (heart failure, epileptic seizure, aspiration pneumonia, etc.) when they reach adulthood. While pediatricians may not be adequately equipped to treat the adult medical needs of these patients, healthcare professionals and hospitals specializing in the care of adult patients may have insufficient expertize to manage adult symptoms of conditions emerging in childhood (6).

In our country, the Ministry of Health considers individuals under the age of 18 as children. The Ministry recommends that pediatric patients should be treated in pediatric ICUs; however, if there is no space available, they should be admitted to adult ICUs (7). In routine practice, children taken to adult ICUs are transferred to pediatric ICUs as soon as possible because of the conditions. However, when children with childhood-onset chronic disease (CCD) reach the age at which they should be accepted as adults, they are admitted to the adult ICU due to the payment terms of "Social Health Insurance". However, despite the increasing age of these children, some of them are still considered children in terms of physical development. In these patients, physiological and developmental differences require different approaches in drug and fluid therapies, drug doses, cardiopulmonary resuscitation, and safety. The characteristics of these patients who are admitted to ICUs should be well known to prepare for the increase in the number of adults with chronic diseases starting in childhood. However, very few studies have focused on adults living in spite of CCD and hospitalized in the ICU (8,9). Until now, there has not been any study conducted in our country on the status of these patients treated in ICUs managed by physicians and nurses specialized in adult patient treatment.

The aim of this study was to evaluate the demographic characteristics of patients with CCD admitted to the adult ICU, the reasons for admission to the ICU, treatment processes, and treatment results.

METHODS

After the approval of the University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee (decision no: 2011-KAEK-25 2020/06-24, date: 24.06.2020), the files of patients who were hospitalized in the adult ICU between June 1, 2010 and May 31, 2020 were scanned in electronic records. Chronic diseases that started in childhood were identified using the International Statistical Classification of Diseases and Related Health Problems 10 codes. Demographic data of the patients, chronic diseases diagnosed in childhood, coexisting diseases, ICU admission diagnosis, ICU hospitalization place (emergency room, clinic, operating room), Glasgow coma score, Acute Physiology and Chronic Health Evaluation (APAHCE) II score, and status of ICU hospitalization before were recorded.

Treatments applied to patients in the ICU and their durations mask-nasal oxygen, noninvasive/invasive mechanical ventilation (NIMV/IMV), endotracheal intubation, opening tracheostomy, extracorporeal treatments [renal replacement therapy (RRT), plasmapheresis, selective bilirubin apheresis, extracorporeal membrane oxygenation (ECMO)], route of nutrition administration (oral/nasogastric, gastrostomy, parenteral), length of ICU stay, and treatment outcome (death, discharge) were saved.

The basic life conditions of the patients (not dependent, partially dependent and fully dependent) and the presence of contractures were evaluated.

Statistical Analysis

The IBM SPSS ver. 22.0 (SPSS Inc.; Armonk, NY, USA) program was used for statistical evaluation. The Shapiro-Wilk test was used to examine whether the data were compatible with the normal distribution. Descriptive statistics for numerical variables are expressed as mean ± standard deviation or median ± interquartile range for quantitative data, frequency and percentage (%) for qualitative data. The t-test was used to evaluate the significance of variations and to compare quantitative variables, and the Mann-Whitney test was used to compare quantitative variables with abnormal distribution. Qualitative variables were evaluated using the chi-square (χ^2) test. Results were evaluated at 95% confidence interval and $p<0.05$ was considered significant.

RESULTS

During the study period, 75 patients with CCD were admitted to the adult ICU. Six patients were admitted to the ICU on different dates. Only the first hospitalizations of these patients were included in the study, and evaluation was performed for 69 patients. The patients were a median age of 24 (21-30.5) years, and 43.5% of them were women. The most common CCD was CP (27.5%) and the most common comorbid disease was epilepsy (23.2%). Patients were frequently admitted to the ICU with more than one

diagnosis, and the most common ICU diagnosis was pneumonia (40.6%) and status epilepticus (18.8%). Forty (58%) patients were admitted from the emergency room, 19 (27.5%) from in-hospital clinics, 8 (11.6%) from the operating room, and 2 (2.9%) from the pediatric ICU. APACHE-II was calculated as the prognostic ICU hospitalization score in all patients, and the expected mortality was found to be 32.65±3.96% with a mean score of 16.59±5.24. The actualized ICU mortality was 27.53% (n=19). The difference between the expected and actual mortality rates was statistically significant (p=0.004). Demographic data, ICU admission data, and clinical characteristics are given in Table 1.

Endotracheal intubation was performed in 45 patients. Difficult intubation was encountered in 4 of them. Video laryngoscopy was used in 3 of these patients, and fiberoptic bronchoscopy was used in 1 patient. A total of 18 patients underwent tracheostomy. Of these, 14 underwent percutaneous tracheostomy and 4 underwent surgical tracheostomy, which was performed by otolaryngologists. Three patients had a tracheostomy cannula when they were admitted to the ICU. IMV was applied to 48 patients for follow-up. During ICU treatment RRT was administered to 15 patients. Bilirubin apheresis was also applied to 2 of the patients who underwent RRT, and plasmapheresis was also applied to 1 of them. Bilirubin apheresis was performed to treat acute liver failure. Continuous RRT had to be applied to 4 patients with unstable hemodynamics. In addition, ECMO support was provided to 3 patients, one of whom had continuous RRT during ECMO. The treatments applied to the patients and their durations are shown in Tables 2 and 3.

The nutrition of the patients was mostly provided by a nasogastric tube (47.5%). Four patients underwent percutaneous endoscopic gastrostomy (PEG) on admission to the ICU; one of them had to be removed because of infection. PEG was performed in three patients during their treatment in the ICU (Table 2).

In the ICU routine, while family members' visits were limited to once a day, the families of these patients were allowed to visit at least three times a day.

Patients were discharged to in-hospital clinics most frequently (60%) after ICU treatment. Ten (52.6%) of 19 patients who died were lost due to sepsis (Table 4). There was no significant relationship between CCD and ICU mortality (p=0.1). The mortality of the patients whose reasons of hospitalization were pneumonia, sepsis, and post-cardiac arrest was found to be significantly higher than the other hospitalization diagnoses (p<0.05, p<0.05, p<0.01, respectively).

Table 1. Demographic data of patients and disease diagnosis

	ICU patients (n=69)
Gender (F/M), (n), (%)	30/39 (43.5/56.5)
Age (year) (median) (IQR)	24 (21-30.5)
APACHE-II score (mean ± SD)	16.59±5.24
GCS (median) (IQR)	10 (8.5-14)
Diagnosis of admission to ICU n (%)*	100 (100)
Pneumonia	28 (40.6)
Status epilepticus	13 (18.8)
Acute respiratory failure	12 (17.3)
Renal failure	11 (15.9)
Post-cardiac arrest	11 (15.9)
Diabetic ketoacidosis	8 (11.6)
Post-operative respiratory failure	5 (7.2)
Sepsis	5 (7.2)
ARDS	2 (2.9)
Post-operative bleeding	3 (4.3)
Others	2 (2.9)
Childhood-onset chronic disease n (%)	69 (100)
Cerebral palsy	19 (27.5)
Diabetes mellitus type I	11 (15.9)
Chromosomal genetic abnormality	9 (13)
Immune deficiency	8 (11.6)
Cystic fibrosis	5 (7.2)
Epilepsy	3 (4.3)
Congenital muscular dystrophies	3 (4.3)
Familial Mediterranean fever	2 (2.9)
Primer sclerosing cholangitis	2 (2.9)
Congenital cardiac disease	2 (2.9)
Lymphoma	2 (2.9)
Meningomyelocele	1 (1.4)
Thalassemia major	1 (1.4)
Comorbidity n (%)*	60 (100)
Epilepsy**	16 (26.6)
Mental retardation	12 (20)
Chronic renal failure	10 (16.7)
Hypertension	6 (10)
Chronic lung disease	6 (10)
Other	10 (16.7)

ICU: Intensive care unit, F/M: Famele/male, IQR: Interquartile range, SD: Standard deviation, APACHE: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow coma scale, ARDS: Acute respiratory distress syndrome, CPR: Cardiopulmonary resuscitation
*A patient may have more than one hospitalization diagnosis
**Childhood disease not diagnosed with epilepsy

High mortality was encountered in those with a diagnosis of cystic fibrosis (4 out of 5 patients=80%). It was found that these patients were admitted to the ICU due to respiratory failure and pneumonia, that 3 of them died from hypoxemia, and one of them died from heart failure in a median period of 6 days (minimum 2-maximum 10).

Mortality rates were significantly higher in patients with comorbid diseases such as chronic lung disease or mental retardation ($p<0.05$). The durations of ICU stay and respiratory support belonging to those who were discharged and those who died were similar ($p>0.05$).

When the basic life conditions of the patients during their hospitalizations were examined, it was found that 26 (37.7%) patients were completely dependent, 13 (18.8%) were partially dependent, and 30 (43.5%) patients were independent. There was no significant relationship between basic life situations and mortality. In addition, 6 (8.7%) patients had severe contractures of the extremities during ICU hospitalization.

Table 2. ICU supportive treatment of patients*

	ICU patients (n=69)
Oxygen therapy, n (%)	44 (100)
Mask	39 (88.7)
Nasal cannula	3 (6.8)
HFNO	2 (4.5)
Mechanical ventilation, n (%)	54 (100)
IMV	48 (88.9)
NIMV	6 (11.1)
Nutrition, n (%)	69 (100)
NG	33 (47.8)
Oral	11 (15.9)
Oral + NG	11 (15.9)
PN + NG	8 (11.6)
PEG	6 (8.7)
Extracorporeal treatment, n (%)	21 (100)
RRT	15 (71.4)
ECMO	3 (14.3)
Bilirubin apheresis	2 (9.5)
Plasmapheresis	1 (4.8)

ICU: Intensive care unit, IQR: Interquartile range, HFNO: High-flow nasal oxygen, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation, NG: Nasogastric tube, PN: Parenteral nutrition, PEG: Percutaneous endoscopic gastrostomy, RRT: Renal replacement therapy, ECMO: Extracorporeal membrane oxygenation
*More than one supportive treatment was applied to a patient

Table 3. Duration of supportive treatments and ICU length of stay

	ICU patients (n=69)
Endotracheal intubation (day) median (IQR)	12 (6-23)
Oxygen therapy	
Mask (day), median (IQR)	3.5 (2-8)
Nasal (day), mean ± SD	16.33±10.01
HFNO (day), mean ± SD	2±0
NIMV (day), mean ± SD	3.16±1.94
IMV (day), median (IQR)	19.5 (5.75-44)
ICU LOS (day), median (IQR)	19 (6.5-45)

ICU: Intensive care unit, IQR: Interquartile range, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation, HFNO: High-flow nasal oxygen, SD: Standard deviation, LOS: Length of stay

Table 4. Discharge and mortality status of patients

	ICU patients (n=69)
Mortality n (%)	19 (27.5)
Cause of death n (%)	19 (100)
Sepsis	10 (52.6)
Hypoxemia	4 (21.1)
Multi-organ failure	2 (10.5)
Acute liver failure	2 (10.5)
Hearth failure	1 (5.3)
Discharge n (%)	50 (100)
Clinics	30 (60)
Palliative service	11 (22)
Home	9 (18)

ICU: Intensive care unit

DISCUSSION

Our study on the treatment of CCDs in "adult ICUs" is the first study from our country on this subject. In our study, we found that these patients were most frequently admitted to the ICU with a diagnosis of pneumonia, that the most common CCD was CP, and that ICU treatments resulted in 27.5% mortality.

Nowadays, because more children with chronic diseases that start in childhood reach adult age, there is a need for healthcare professionals and hospitals that can manage both their CCDs and adult diseases that can occur with age. For example, cardiovascular diseases (CVDs), which we could not see in patients with CP years ago, are now seen today as they reach adulthood (2). In this case, the clinics where the patient is hospitalized should be sufficient for

the management of CVDs and CP. In addition, it is unclear in which clinics both such patients and patients situated between children and adults should be treated. Balancing subspecialty care with age-appropriate care is difficult. Goodman et al. (4) examined adult patients with CCD who were hospitalized in a children's hospital between 1999 and 2008 and found that 2.8% of all hospitalizations were over 18 years old [transitional (2.0%): 18-21, adult (0.8%): aged>21]. The authors reported that the most common reason for hospitalization was congenital heart disease, followed by malignant neoplasms. Loveday et al. (1) stated that when looking at adult and pediatric ICU admissions of teenagers aged 16-19, although those with congenital and neuromuscular disorders are hospitalized in pediatric ICU, admission diagnoses in adult ICU were trauma and diabetic ketoacidosis. In our study, we examined patients over 18 years of age with only a CCD diagnosis in the adult ICU. We determined that the 3 most common primary CCD diagnoses were CP, diabetes mellitus (DM) type I, and chromosomal/genetic diseases. While pneumonia was the most common cause of ICU admission, 11.6% of the patients were admitted to the adult ICU with the diagnosis of diabetic ketoacidosis.

It was reported that patients diagnosed with CP may have hospital and ICU admission requirements for reasons such as aspiration pneumonia, pressure sores, and status epilepticus until reaching adulthood and after. Similarly, in our study, we found that patients with the most frequent diagnosis of CP were admitted to the ICU with a diagnosis of status epilepticus and pneumonia (10). Mcphee et al. (11) in their systematic reviews based on 19 studies on adult CP patients showed some evidence that the prevalence of CVD increases with age in these patients and that there is an increased risk of death due to certain risk factors such as hypertension, obesity, and CVD. In our study, we found that 4 patients diagnosed of CP died because of ICU treatment. Although the relationship between deaths and CVD could not be determined, hypertension was in 3 patients as a concomitant disease.

The majority of patients diagnosed with cystic fibrosis reach adulthood today, and in a period of their lives, they may require ICU hospitalization because of pulmonary and gastrointestinal system problems (3,12). The median age of these patients is prolonged up to 40 years, and short-term ventilation support may be required after elective surgical operations such as opening a gastrostomy (12). Siuba et al. (13) found a mortality rate of 44.5% in adults with cystic fibrosis who required mechanical ventilation. In our study, 5 patients diagnosed with cystic fibrosis were admitted to the ICU. One of these patients was taken to the ICU postoperatively, and the other four patients were diagnosed with respiratory failure due to pneumonia. Unfortunately, 80% of our patients who received IMV support died.

In fact, in everyday medical practice, the answer to the question "Can adult ICUs adequately meet the care needs of pediatric-looking patients due to growth retardation with CCD?" is essential. Today, as increasing numbers of children with chronic diseases survive into adulthood, it is unclear whether pediatric or adult ICUs are the best place to meet the critical care needs of these patients or not. In a study, it was found that, 19-40 years-old adult patients with CCD, except for type I diabetes, were hospitalized more frequently in pediatric ICUs. The authors suggested that as the number of these patients increased, pediatric ICUs should gradually be prepared for older patients and/or adult ICUs should be able to meet the care needs of these patients (2). In another study by the same authors, it was found that those in their early 20s (20-22 years) were admitted to the pediatric ICU and 25-32 years old individuals were admitted to the adult ICU. In this study, it was observed that patients with CCD are mostly admitted to the pediatric ICU (5).

Because family dependency is high in patients with CCD, it should not be forgotten that the role of the family may be different in the treatment process in such patients in the ICU, and hospitalization in a separate child-oriented decorated unit should be considered in adult ICUs (14). In our study, a flexible visitation policy was applied to family members.

Patients with CCD may encounter some problems when they reach adulthood and are admitted to the adult ICU. Adult airway equipment (oral-nasal airway, laryngoscope blade, endotracheal tube, laryngeal mask airway, bronchoscope, etc.) may not be suitable for some of these patients who are adult in age and may be child-sized in terms of body surface area and development. Likewise, the doses of all drugs, including intravenous peripheral and central venous catheters, antibiotherapy and sedative-analgesic drugs, and fluid-electrolyte replacement, may differ from those in adult patients. Adult ICU nurses may have difficulties caring for adult patients with a childlike appearance (14,15). However, in a survey conducted by Suzuki et al. (15) about "transitional care" of adolescents and adults with CCD, they found that 73.6% of nurses had no awareness of "transitional care". In this study, both pediatrics and adult nurses stated that pediatricians would be the ideal coordinator for transiting CCD patients from child-focused to adult-focused health care. The improved survival of children with chronic illnesses has led to the necessity of transitioning from pediatric healthcare to adult care for adolescents and

young adults with special healthcare needs. Transfer of care from pediatric to adult providers is vital for young adults with complex health needs. Good communication and collaboration between the pediatric and adult care teams are crucial to reduce the rate of ICU morbidity and mortality (14-16).

It is retrospective and examines patients with a disease that only started in childhood and was treated in the adult ICU. However, these patients can sometimes be treated in the pediatric ICU by pediatricians who have followed the patient since childhood when the disease was diagnosed. Another limitation of this study is that we could not compare the data of patients with the same characteristics who were treated in the pediatric ICU.

CONCLUSION

It should be kept in mind that the life expectancy of patients with CCD is prolonged, that adult ICUs should be prepared for these patients, and that physicians and nurses in the ICU should be trained in the care of patients.

ETHICS

Ethics Committee Approval: University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee approval was obtained (decision no: 2011-KAEK-25 2020/06-24, date: 24.06.2020).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: G.Ç., A.S., H.E.S., N.K.G., Design: G.Ç., A.S., H.E.S., N.K.G., Data Collection or Processing: G.Ç., A.S., H.E.S., N.K.G., Analysis or Interpretation: G.Ç., H.E.S., N.K.G., Literature Search: G.Ç., A.S., H.E.S., N.K.G., Writing: G.Ç., A.S., H.E.S., N.K.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. L Loveday, N Rasburn, M Thomas. Teenagers: paediatric or adult ICU? Crit Care 2009;13:P481.
2. Edwards JD. Cardiovascular disease and other childhood-onset chronic conditions in adults with cerebral palsy. Dev Med Child Neurol 2019;61:859-60.
3. Maher Z, Nance ML. The pediatric patient cared for in the adult ICU. In: Martin N., Kaplan L. editors. Principles of Adult Surgical Critical Care. Springer, Cham; 2016. p: 431-41.
4. Goodman DM, Hall M, Levin A, Watson RS, Williams RG, Shah SS, et al. Adults with chronic health conditions originating in childhood: inpatient experience in children's hospitals. Pediatrics 2011;128:5-13.
5. Edwards JD, Vasilevskis EE, Yoo EJ, Houtrow AJ, Boscardin WJ, Dudley RA, et al. Adults with childhood-onset chronic conditions admitted to US pediatric and adult intensive care units. J Crit Care 2015;30:201-6.
6. Peter NG, Forke CM, Ginsburg KR, Schwarz DF. Transition from pediatric to adult care: internists' perspectives. Pediatrics 2009;123:417-23.
7. Ministry of Health notification on the application procedures and principles of intensive care services in bed healthcare facilities. https://www.resmigazete.gov.tr/eskiler/2015/08/20150816-7.htm
8. Edwards JD, Vasilevskis EE, Houtrow AJ, Dudley R, Okumura MJ. A comparison of mortality and length of stay for adults with childhood chronic conditions treated in pediatric and adultI CUs. Am J Respir Crit Care Med 2012;185:A1474.
9. Edwards JD, Houtrow AJ, Vasilevskis EE, Dudley RA, Okumura MJ. Multi-institutional profile of adults admitted to pediatric intensive care units. JAMA Pediatr 2013;167:436-43.
10. Kuo TJ, Hsu CL, Liao PH, Huang SJ, Hung YM, Yin CH. Nomogram for pneumonia prediction among children and young people with cerebral palsy: A population-based cohort study. PLoS One 2020;15:e0235069.
11. Mcphee PG, Claridge EA, Noorduyn SG, Gorter JW. Cardiovascular disease and related risk factors in adults with cerebral palsy: a systematic review. Dev Med Child Neurol 2019;61:915-23.
12. Fraser J., Campbell M. Teenagers in intensive care: adult or paediatric ICU? Paediatrics and Child Health 2007;17:454-9.
13. Siuba M, Attaway A, Zein J, Wang X, Han X, Strausbaugh S, et al. Mortality in adults with cystic fibrosis requiring mechanical ventilation. Cross-sectional analysis of nationwide events. Ann Am Thorac Soc 2019;16:1017-23.
14. Ibsen LM, Conyers PM, Pate MF. Providing adult and pediatric care in the same unit: multiple considerations. AACN Adv Crit Care 2013;24:117-20.
15. Suzuki S, Kita S, Morisaki M, Kikuchi R, Sato I, Iwasaki M, et al. Nurses' perceptions regarding transitional care for adolescents and young adults with childhood-onset chronic diseases. Jpn J Nurs Sci 2020;17:e12323.
16. Willis LD. Transition from pediatric to adult care for young adults with chronic respiratory disease. Respir Care 2020;65:1916-22.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:302-307
DOI: 10.4274/BMJ.galenos.2023.2023.8-14

Research

Evaluation of Nosocomial Infections in a Tertiary Pediatric Intensive Care Unit

Üçüncü Basamak Bir Pediatrik Yoğun Bakım Ünitesinde Nozokomiyal Enfeksiyonların Değerlendirilmesi

Cansu Durak[1], Ebru Güney Şahin[1], Yaşar Yusuf Can[1], Alican Sarısaltık[2], Kübra Boydağ Güvenç[1], Fatih Varol[1]

[1]University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Clinic of Pediatric Intensive Care, Istanbul, Türkiye
[2]Republic of Türkiye Ministry of Health, Çayırova District Health Directorate, Kocaeli, Türkiye

ABSTRACT

Objective: Nosocomial infections are an important preventable cause of increased morbidity and mortality in critically ill children. Our study compared the clinical features, laboratory data, and prognostic variables of nosocomial infections (NI) in children in the tertiary pediatric intensive care unit (PICU).

Methods: A retrospective evaluation of 48 pediatric patients aged 1 month to 18 years who had been admitted between February 2022 and January 2023 at University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital was performed. Children with NI were included. Demographic clinical and outcome data were analyzed.

Results: Twenty-seven patients (56.3%) were males. The median age was 32 months, and the length of stay in the PICU was 25 days (7-114). Respiratory diseases (50%) were the most common reasons for admission to the PICU, followed by sepsis (22.9%) and trauma (12.5%). The mortality rate was 18.8%. The requirement for renal replasman treatment was significantly higher in the non-survival group (p=0.017). Patients had similar prolonged PICU stay rates and requirements of mechanical ventilation, plasma exchange, and inotropic agents (p=0.472, p=0.320, p=0.432, p=0.068). Procalcitonin (PCT) (p=0.015), and procalcitonin/albumin ratio (PAR) (p=0.016) were also higher in the non-survival group than those in the survival group. Receiver operating characteristic (ROC) curves were used to predict mortality with PCT and PAR. According to ROC analysis, the cut-off values for PCT and PAR were found to be 1.705 (p=0.015), and 0.538 (p=0.016) respectively.

Conclusion: Risk factors that cannot be changed, such as the underlying disease, should be considered in patients. Other modifiable risk factors for NIs will likely be the focus of efforts to enhance patient care.

Keywords: Culture, nosocomial infection, organ dysfunction, pediatrics, sepsis

ÖZ

Amaç: Nozokomiyal enfeksiyonlar (NE), kritik hasta çocuklarda artmış morbidite ve mortalitenin önlenebilir önemli bir nedenidir. Çalışmamız, üçüncü basamak çocuk yoğun bakım ünitesindeki (ÇYBÜ) çocuklarda NE'lerin klinik özelliklerini, laboratuvar verilerini ve prognostik değişkenlerini karşılaştırdı.

Gereç ve Yöntem: Şubat 2022 ve Ocak 2023 tarihleri arasında Sağlık Bilimleri Üniversitesi, Sancaktepe Şehit Prof. Dr. İlhan Varank Eğitim ve Araştırma Hastanesi'ne başvuran 1 ay-18 yaş arası 48 çocuk hastanın retrospektif değerlendirmesi yapıldı. NE olan çocuklar dahil edildi. Demografik veriler, klinik değişkenler ve sonuç verileri analiz edildi.

Bulgular: Yirmi yedi hasta (%56,3) erkekti. Ortanca yaş 32 aydı ve ÇYBÜ'de kalış süresi 25 gündü (7-114). En sık başvuru nedeni solunum yolu hastalıkları (%50) olurken, bunu sepsis (%22,9) ve travma (%12,5) takip etti. Mortalite oranı %18,8 idi. Renal replasman tedavisi gereksinimi sağ kalamayan grupta anlamlı olarak daha yüksekti (p=0,017). Hastaların benzer uzamış ÇYBÜ kalış oranları ve mekanik ventilasyon, plazma değişimi ve inotropik ajan gereksinimleri vardı (p=0,472, p=0,320, p=0,432, p=0,068). Prokalsitonin (PCT) (p=0,015) ve prokalsitonin/albumin oranı (PAR)

Address for Correspondence: Cansu Durak, University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Clinic of Pediatric Intensive Care, Istanbul, Türkiye
Phone: +90 535 338 05 11 E-mail: bzmrt@hotmail.com ORCID ID: orcid.org/0000-0002-2424-6887

Cite as: Durak C, Güney Şahin E, Can YY, Sarısaltık A, Boydağ Güvenç K, Varol F. Evaluation of Nosocomial Infections in a Tertiary Pediatric Intensive Care Unit. Med J Bakirkoy 2023;19:302-307

Received: 19.08.2023
Accepted: 04.09.2023

(p=0,016) da yaşamayan grupta yaşayan gruba göre daha yüksekti. PCT ve PAR ile mortaliteyi tahmin etmek için alıcı işletim karakteristik (ROC) eğrileri kullanıldı. ROC analizine göre PCT ve PAR için cut-off değerleri sırasıyla 1,705 (p=0,015) ve 0,538 (p=0,016) olarak bulundu.

Sonuç: Hastalarda altta yatan hastalık gibi değiştirilemeyen risk faktörleri göz önünde bulundurulmalıdır. NE'ler için diğer değiştirilebilir risk faktörleri, muhtemelen hasta bakımını iyileştirme çabalarının odak noktası olacaktır.

Anahtar Kelimeler: Kültür, nozokomiyal enfeksiyon, organ disfonksiyonu, pediatri, sepsis

INTRODUCTION

Nosocomial infection (NI) is a prevalent global health problem, particularly in pediatric intensive care units (PICU), and is associated with high mortality and morbidity, prolonged hospital stays, and high costs (1,2). There are numerous risk factors for NIs in critically ill children. In PICUs, there is frequent utilization of invasive medical devices, including endotracheal tubes (ETTs), central venous catheters (CVCs), and urine catheters. It is well-recognized that these devices increase the risk of NI (3).

The risk of nosocomial sepsis among critically ill children hospitalized in the PICU for more than two weeks is 50%. Although prevention bundles can reduce NI rates, this risk cannot be eliminated (4). Patients with NIs were found to have higher rates of poor outcomes and organ dysfunction. The overall mortality rate of NIs in children is estimated to be 11% (5). However, different factors, such as the presence of multiresistant microorganisms, affect prognosis, as shown in the literature (6).

Our study compared the clinical and demographic characteristics, laboratory parameters, and prognostic factors of NIs in children hospitalized in tertiary PICUs.

METHODS

This retrospective study was conducted in the PICU at Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, University of Health Sciences Türkiye. Healthcare provision for children aged from 1 month to 18 years is provided in our PICU, which is equipped with 12 beds, 12 ventilators, 5 Prismaflex™ hemofiltration machines (Baxter, USA), and 9 isolation rooms.

A retrospective evaluation of 48 pediatric patients aged 1 month to 18 years who had been admitted between February 2022 and January 2023, if they met the criteria for NI, was included in the study. Patients who did not meet these criteria were excluded from the study. In our 12-bed PICU, 456 patients were hospitalized and followed up during the study period.

The Center for Disease Control criteria were used for the diagnosis of NI. An infection was defined as nosocomial when it occurred 48 hours (h) after admission to the PICU, and there was no evidence that the infection was present or incubated at the time of admission to the PICU. Children were evaluated for catheter-related bloodstream infection (CRBSI), ventilator-associated pneumonia (VAP), and catheter-associated urinary tract infections (CAUTI) (7).

CRBSI was defined as 2 positive blood cultures and the presence of one of the following symptoms in the case of a positive blood culture for a known pathogen unrelated to an infection at another site or commensal organisms: fever (>38 °C), chills at the insertion site, hypotension, or the appearance of infection. To be included in this study, the patient had to have a CVC within 48 h before this event (5).

We obtained informed consent from all parents before hospitalization and during all procedures. University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Non-invasive Research Ethics Committee approval was obtained from the hospital (decision no: 29, date: 15.02.2023). This study was conducted in accordance with the ethical rules of the Declaration of Helsinki Principles.

A detailed form was used for data collection regarding the patient's age, gender, length of stay in the PICU, duration of invasive mechanical ventilation (IMV), extracorporeal treatment requirement, inotropic treatment, laboratory parameters on the day of NI detection, treatment outcomes, and mortality. The blood sampling data of all cases were measured at almost the same time from the onset, and the worst value in the first 24 h of admission was recorded. Complete blood count, serum albumin, lactate dehydrogenase; procalcitonin (PCT), C-reactive protein (CRP) levels, and blood gas analysis on admission were retrospectively recorded from our electronic health information system. For the calculation of the Pediatric Risk of Mortality III (PRISM III) score, data from 16 variables regarding temperature, systolic blood pressure, heart rate, partial pressure of arterial oxygen, partial pressure of arterial carbon dioxide, Glasgow coma score, pupillary reaction, prothrombin time and activated partial thromboplastin time, serum creatinine, serum urea nitrogen, serum potassium, blood glucose, and serum bicarbonate levels, white blood cell and platelet counts were recorded within 24 h of PICU admission (8).

To detect pathogens in patients, double blood cultures were obtained from two sites at admission, and other biological samples were also collected for culture, including sputum, pleural effusion, ascites, urine, feces, pus, and others, according to the suspected infection site. Double blood cultures, including those of the CVC and peripheral vein, were taken in patients with suspected catheter infection. The volume of blood collected was determined according to the weight of the patient (9).

For the diagnosis of VAP, tracheobronchial samples were collected via deep tracheal aspirates from ETTs using a closed aspiration technique, and urine samples were aseptically aspirated from the urinary catheter sampling port. The number of colony-forming units (CFU/mL) in urine culture was considered to be more than 10^5 CFU/mL (7).

Statistical Analysis

SPSS statistical software 20.0 for Windows was used for statistical analyzes numbers, frequencies (%), ratios, medians, and standard deviation values were used in the descriptive statistics of the data. The distribution of variables was checked using the Kolmogorov-Smirnov test. During the analysis of quantitative data, t-tests and Mann-Whitney U tests were used. The $\chi 2$ test was used to compare categorical variables, and the Fisher Exact test was used when chi-square conditions could not be met.

RESULTS

During the study period, 48 of 456 patients with NI were included. The gender distribution was about equal. The median age of the patients was 32 months. Respiratory diseases (50%) such as pneumonia and asthma attacks were the most common reasons for admission to the PICU, followed by sepsis (22.9%) and trauma (12.5%). The median length of stay in the PICU was 25 days, ranging from 7 to 114 days, and 93.8% had hospitalizations longer than 7 days. The median PRISM III score was 8 (0-30). IMV was required in 41 patients (85.4%), and the median duration of IMV was 13 (3-102) days. Inotropic agents were used in 23 patients (47.9%). Fifteen patients (31.3%) underwent therapeutic plasma exchange (TPE), and 7 patients (14.6% of the total) had continuous renal replacement therapy (CRRT) (Table 1).

The most common pathogens identified were Gram-negative bacteria (33.3%) and fungus (27.1%) (Table 1). The rates of CRBSI, VAP, and CAUTI were 56.2%, 25%, and 18.7%, respectively (Table 2). The most frequent pathogens were *Pseudomonas aeruginosa*, *Klebsiella* species, and *Candida* species.

The mortality rate was 18.8%. According to the prognostic outcome in the PICU, patients were divided into the survival group (n=39) and the non-survival group (n=9). The requirement for CRRT was significantly higher in the non-survival group (p=0.017). Patients had similar prolonged PICU stay rates and requirements of IMV, TPE, and inotropic agents (p=0.472, p=0.320, p=0.432, p=0.068) (Table 3). PCT (p=0.015), and procalcitonin/albumin ratio (PAR) (p=0.016) were also higher in the non-survival group than those in the survival group (Table 4). Receiver operating characteristic

Table 1. Demographics, clinical characteristics of children with nosocomial infections

		n=48
Gender, n (%)	Male	27 (56.3%)
	Female	21 (43.8%)
Age (month), median (min-max)		32 (1.5-214)
PRISM III score		8 (0-30)
Etiologies of admission, n (%)	Respiratory diseases	24 (50%)
	Sepsis	11 (22.9%)
	Trauma	6 (12.5%)
	Neurological diseases	3 (6.3%)
	Other	4 (8.4%)
Mortality, n (%)		9 (18.8%)
Length of stay (day), median (min-max)		25 (7-114)
Length of stay >7 days, n (%)		45 (93.8%)
Requirement of IMV, n (%)		41 (85.4%)
Duration of IMV, days median (min-max)		13 (3-102)
Requirement of TPE, n (%)		15 (31.3%)
Requirement of CRRT, n (%)		7 (14.6%)
Requirement of inotropic agents, n (%)		23 (47.9%)
Pathogens, n (%)	Gram-positive bacteria	6 (12.5%)
	Gram-negative bacteria	16 (33.3%)
	Fungus	13 (27.1%)
	Multiple pathogens	12 (25.0%)

CRRT: Continuous renal replacement therapy, IMV: Invasive mechanical ventilation, PRISM III: Pediatric Risk of Mortality III, TPE: Therapeutic plasma exchange, min-max: Minimum-maximum

Table 2. Types of nosocomial infections

	n (%)
CRBSI	27 (56.2%)
VAP	12 (25%)
CAUTI	9 (18.7%)

CAUTI: Catheter-associated urinary tract infections, CRBSI: Catheter-related bloodstream infection, VAP: Ventilator-associated pneumonia

(ROC) curves were used to predict mortality with PCT and PAR. According to ROC analysis, the cut-off values for PCT and PAR were found to be 1.705 (p=0.015), and 0.538 (p=0.016) respectively (Table 5, Figure 1).

Table 3. Treatment modalities according to sepsis outcomes

	Outcome		p-value
	Mortality, n (%) (n=9)	Survival, n (%) (n=39)	
Length of stay >7 days	8 (17.8%)	39 (81.3%)	0.472
Requirement of IMV	9 (22.0%)	32 (78.0%)	0.32
Requirement of CRRT	4 (57.1%)	3 (42.9%)	**0.017**
Requirement of TPE	4 (26.7%)	11 (73.3%)	0.432
Requirement of inotropic agents	7 (30.4%)	16 (69.6%)	0.068

CRRT: Continuous renal replacement therapy, IMV: Invasive mechanical ventilation, TPE: Therapeutic plasma exchange

DISCUSSION

Children admitted to the PICU are particularly susceptible to NIs because of the high prevalence of the use of invasive devices during their hospitalization (10). NI is a significant cause of morbidity and mortality as well as a serious financial burden. The overall incidence of NI in our PICU was 10.5%, similar to the results reported in other studies. As in most pediatric studies, we found CRBSI to be the most frequent NI (11-13).

We found that Gram-negative bacteria and fungus were more common in NI. Several studies have found that Gram-negative bacteria are more frequently isolated than Gram-positive bacteria, despite conflicting findings regarding pathogens (14). The reason for the high incidence of fungal infections in this study may be the inclusion of atypical agents.

Table 4. Relationship between laboratory parameters and outcomes of sepsis patients

	Outcome		p-value
	Mortality, n (%) (n=9)	Survival, n (%) (n=39)	
Leukocyte	7850 (4660-23790)	10160 (50-34930)	0.061
Neutrophil	6160 (2700-21830)	7350 (0-32680)	0.342
Lymphocyte	1380 (810-2930)	1810 (0-7170)	0.240
Platelet	246000 (55000-327000)	242000 (7000-724000)	0.452
RDW	15.3 (14.7-18.3)	14.4 (11.4-20.0)	0.037
CRP	54.97 (0.6-229.23)	9.97 (0.04-386.11)	0.376
Procalcitonin	11 (0.23-334.24)	0.53 (0.03-315.52)	**0.015**
Lactate	1.27 (0.6-4.3)	1.5 (0.4-19.3)	0.711
LDH	489 (296-3340)	389 (173-2133)	0.178
Albumin	3.21 (1.97-3.98)	3.6 (1.2-4.73)	0.079
Lactate/albumin ratio	0.47 (0.15-1.63)	0.43 (0.1-5.24)	0.436
Neutrophil/lymphocyte ratio	4.10 (1.56-19.85)	2.93 (0.68-102.13)	0.516
CRP/albumin ratio	16.47 (0.15-96.32)	2.65 (0.01-153.05)	0.322
PCT/albumin ratio	3.23 (0.11-92.33)	0.171 (0.008-113.90)	**0.016**
LDH/albumin ratio	151.7 (77.8-1403.3)	106.4 (48.7-725.5)	0.11

CRP: C-reactive protein, LDH: Lactate dehydrogenase, PCT: Procalcitonin, RDW: Red cell distribution width

Table 5. Predictive characteristics of markers

	Cut-off threshold	Sensitivity (%)	Specificity (%)	AUC (95.0% CI)	p-value
Procalcitonin	1.705	77.8	66.7	0.764 (0.605-0.922)	0.015
PAR	0.538	77.8	64.1	0.761 (0.604-0.918)	0.016

AUC: Area under curve, PAR: Procalcitonin to albumin ratio, CI: Confidence interval

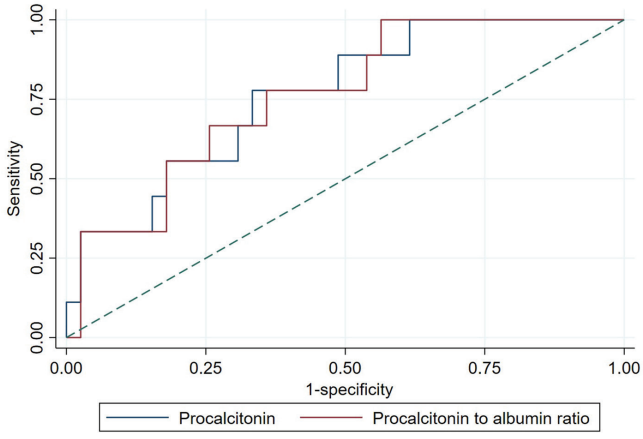

Figure 1. Analysis of ROC curves of mortality and biomarkers
ROC: Receiver operating characteristic

Most patients had prolonged stays in the PICU. This result was consistent with the literature and could be explained by the lengthier stay, more frequent invasive operations, and increased patient contact with medical staff (15,16). Furthermore, the adverse hemodynamic consequences of NI may worsen organ dysfunction in critically ill pediatric patients and escalate the requirement for supportive care (3).

Mortality of NI in our study was 18.8%, which is similar to that reported in developing countries and higher than that reported in developed counties. Mortality rates in developing countries ranged from 20% to 38%, whereas they were 7.7 % to 10% in developed countries (11,14,17-19).

Another remarkable aspect of our data is that there was no statistically significant difference when comparing non-survival and survival patients for other treatment modalities. The adverse hemodynamic consequences of NI may worsen organ dysfunction in critically ill pediatric patients and escalate the requirement for supportive care (3). There were not significant differences in terms of the length of PICU stay, requirement of TPE, or inotropic agents. However, non-survival patients had a greater requirement for CRRT. Presumably, in terms of the requirement of these treatment modalities, patients with NI should be fully compared with patients hospitalized in the PICU.

Along with cultures, conventional and widespread biomarkers, such as CRP and leukocyte count, are generally regarded as valuable for the diagnosis of infection (20). This particular approach is considered insufficient for early diagnosis because it may take between 24 and 72 h to obtain culture results. Given that delays in diagnosis may increase the risk of mortality, it is necessary to develop quicker and more effective diagnostic markers.

PCT demonstrated a high level of accuracy in predicting the presence of bacteremia in cases of infection. Consequently, it is advisable to use PCT in the assessment of bacterial infection and sepsis among critically ill patients because it has been found to potentially correlate with poor outcomes in patients (21-23). Moreover, albumin serves as a robust indicator of clinical disease outcomes because of its tendency to decrease during acute infections (24,25). There is a significant correlation between PCT and albumin. Therefore, the co-occurrence of PCT positivity and albumin negativity serves as a prognostic indicator in adult patients susceptible to bacterial infection. Some studies have suggested that PAR is a rapid and relatively inexpensive biomarker that can be used as an early marker to differentiate severe NIs (20,26). Consistent with the literature, we found that PCT levels and PAR of non-survival patients were significantly higher than those of survival patients.

The main limitations of this study were the small number of cases compared with studies in adults and the inclusion of only one tertiary center. The inclusion of multiplecenters could provide additional information and identify other prognostic factors in NIs among children. Second, the low positivity and lack of standardization in culture collection time may have affected the results of pathogen identification. Furthermore, our study did not describe all NIs, such as surgical incision infections.

CONCLUSION

NIs are an important preventable cause of increased morbidity and mortality in critically ill children. This prompts the question, as clinicians, of what we can do to reduce NIs. Risk factors should be considered in patients who cannot be changed, such as the underlying disease. Other modifiable risk factors for NIs will likely be the focus of efforts to enhance patient care.

ETHICS

Ethics Committee Approval: University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Non-invasive Research Ethics Committee approval was received from the hospital (decision no: 29, date: 15.02.2023).

Informed Consent: We obtained informed consent from all parents before hospitalization and during all procedures.

Authorship Contributions

Concept: C.D., K.B.G., Design: K.B.G., Data Collection or Processing: E.G.Ş., Y.Y.C., Analysis or Interpretation: C.D., A.S., Literature Search: C.D., E.G.Ş., Y.Y.C., Writing: C.D., F.V.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Abramczyk ML, Carvalho WB, Carvalho ES, Medeiros EA. Nosocomial infection in a pediatric intensive care unit in a developing country. Braz J Infect Dis 2003;7:375-80.
2. Deep A, Ghildiyal R, Kandian S, Shinkre N. Clinical and microbiological profile of nosocomial infections in the pediatric intensive care unit (PICU). Indian Pediatr 2004;41:1238-46.
3. Sribnick EA, Hensley J, Moore-Clingenpeel M, Muszynski JA, Thakkar RK, Hall MW. Nosocomial Infection Following Severe Traumatic Injury in Children. Pediatr Crit Care Med 2020;21:443-50.
4. Hall MW, Knatz NL, Vetterly C, Tomarello S, Wewers MD, Volk HD, et al. Immunoparalysis and nosocomial infection in children with multiple organ dysfunction syndrome. Intensive Care Med 2011;37:525-32.
5. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in pediatric intensive care units in the United States. National Nosocomial Infections Surveillance System. Pediatrics 1999;103:e39.
6. Dabar G, Harmouche C, Salameh P, Jaber BL, Jamaleddine G, Waked M, et al. Community- and healthcare-associated infections in critically ill patients: a multicenter cohort study. Int J Infect Dis 2015;37:80-5.
7. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128-40.
8. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med 1996;24:743-52.
9. Hazwani TR, Kazzaz YM, Alsugheir S, Aldelaijan S, Alsugheir F, Alali H, et al. Association Between Culture-Negative Versus Culture-Positive Sepsis and Outcomes of Patients Admitted to the Pediatric Intensive Care Unit. Cureus 2020;12:e9981.
10. Esteban E, Ferrer R, Urrea M, Suarez D, Rozas L, Balaguer M, et al. The impact of a quality improvement intervention to reduce nosocomial infections in a PICU. Pediatr Crit Care Med 2013;14:525-32.
11. Urrea M, Pons M, Serra M, Latorre C, Palomeque A. Prospective incidence study of nosocomial infections in a pediatric intensive care unit. Pediatr Infect Dis J 2003;22:490-4.
12. Becerra MR, Tantaleán JA, Suárez VJ, Alvarado MC, Candela JL, Urcia FC. Epidemiologic surveillance of nosocomial infections in a Pediatric Intensive Care Unit of a developing country. BMC Pediatr 2010;10:66.
13. Grohskopf LA, Sinkowitz-Cochran RL, Garrett DO, Sohn AH, Levine GL, Siegel JD, et al. A national point-prevalence survey of pediatric intensive care unit-acquired infections in the United States. J Pediatr 2002;140:432-8.
14. Raymond J, Aujard Y. Nosocomial infections in pediatric patients: a European, multicenter prospective study. European Study Group. Infect Control Hosp Epidemiol 2000;21:260-3.
15. Delgado-Rodríguez M, Bueno-Cavanillas A, López-Gigosos R, de Dios Luna-Castillo J, Guillén-Solvas J, Moreno-Abril O, et al. Hospital stay length as an effect modifier of other risk factors for nosocomial infection. Eur J Epidemiol 1990;6:34-9.
16. Singh-Naz N, Sprague BM, Patel KM, Pollack MM. Risk factors for nosocomial infection in critically ill children: a prospective cohort study. Crit Care Med 1996;24:875-8.
17. Alotaibi MG, Rahman S, Al-Shalaan MA, Omair A. Frequency of Nosocomial Infections in Pediatric Intensive Care Unit at King Abdulaziz Medical City, Riyadh, Saudi Arabia. J Infect Dis Ther 2015;3:234-6.
18. van Gestel A, Bakker J, Veraart CP, van Hout BA. Prevalence and incidence of severe sepsis in Dutch intensive care units. Crit Care 2004;8:R153-62.
19. El-Sahrigy SAF, Shouman MG, Ibrahim HM, Rahman AMOA, Habib SA, Khattab AA, et al. Prevalence and Anti-Microbial Susceptibility of Hospital Acquired Infections in Two Pediatric Intensive Care Units in Egypt. Open Access Maced J Med Sci 2019;7:1744-9.
20. Deng S, Gao J, Zhao Z, Tian M, Li Y, Gong Y. Albumin/Procalcitonin Ratio Is a Sensitive Early Marker of Nosocomial Blood Stream Infection in Patients with Intra-Cerebral Hemorrhage. Surg Infect (Larchmt) 2019;20:643-9.
21. Ljungström L, Pernestig AK, Jacobsson G, Andersson R, Usener B, Tilevik D. Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. PLoS One 2017;12:e0181704.
22. Riedel S, Melendez JH, An AT, Rosenbaum JE, Zenilman JM. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. Am J Clin Pathol 2011;135:182-9.
23. Pan YP, Fang YP, Xu YH, Wang ZX, Shen JL. The Diagnostic Value of Procalcitonin Versus Other Biomarkers in Prediction of Bloodstream Infection. Clin Lab 2017;63:277-85.
24. Artero A, Zaragoza R, Camarena JJ, Sancho S, González R, Nogueira JM. Prognostic factors of mortality in patients with community-acquired bloodstream infection with severe sepsis and septic shock. J Crit Care 2010;25:276-81.
25. Morotti A, Marini S, Lena UK, Crawford K, Schwab K, Kourkoulis C, et al. Significance of admission hypoalbuminemia in acute intracerebral hemorrhage. J Neurol. 2017;264:905-11.
26. Luo X, Yang X, Li J, Zou G, Lin Y, Qing G, et al. The procalcitonin/albumin ratio as an early diagnostic predictor in discriminating urosepsis from patients with febrile urinary tract infection. Medicine (Baltimore) 2018;97:e11078.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:308-313
DOI: 10.4274/BMJ.galenos.2023.2023.8-13

Research

Appropriateness of the Empirical Antibiotherapy Choices of Primary Care Physicians for the Treatment of Uncomplicated Cystitis

Komplike Olmayan Sistit Tedavisinde Birinci Basamak Hekimlerinin Ampirik Antibiyoterapi Seçimlerinin Uygunluğu

Hakan Polat, Deniz Noyan Özlü

University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Urology, İstanbul, Türkiye

ABSTRACT

Objective: In primary care, the frequency of inappropriate antibiotic prescriptions for urinary tract infections is very high. In this study, we aimed to evaluate the appropriateness of antibiotic choices of primary care physicians for treating uncomplicated cystitis in adult patients considering relevant guidelines.

Methods: The study was conducted with family physicians working in family health centers, general practitioners working as family physicians, and family medicine specialists and assistants working in secondary and tertiary care hospitals in İstanbul between December 2022 and January 2023. Google Forms was used to create a survey for data collection and was distributed to physicians online.

Results: The study included 421 physicians. Among the physicians, the rates of fosfomycin, nitrofurantoin, cephalosporin, sulfonamide, fluoroquinolone (FQ), and penicillin choices were determined to be 83.8% (n=353), 52.3% (n=220), 24% (n=101), 14.5% (n=61), 26.6% (n=112), and 10.7% (n=45). Accepting the use of FQ and aminopenicillin as inappropriate in the first-line treatment of uncomplicated cystitis, younger physicians with shorter tenure were more likely to prescribe appropriate empirical antibiotics (p=0.001). In addition, general practitioners working as family physicians applied inappropriate empirical treatment at a significantly higher rate than family medicine specialists and assistants (39.3% vs. 10% and 11.9%, respectively).

Conclusion: A significant portion of the primary care physicians who participated in this study were determined to prefer antibiotics not recommended in the relevant guidelines for the empirical treatment of uncomplicated cystitis. The higher rates of inappropriate treatment choices of general practitioners and senior physicians in empirical treatment indicate the need for in-service training in primary healthcare services.

Keywords: Primary health care, cystitis, urinary tract infection, anti-bacterial agents

ÖZ

Amaç: Birinci basamak sağlık hizmetlerinde idrar yolu enfeksiyonları (İYE) için uygunsuz antibiyotik reçete edilmesi prevalansı oldukça yüksektir. Bu çalışmada, birinci basamak sağlık hizmeti veren hekimlerin non-komplike sistit ile başvuran erişkinlerde antibiyotik seçiminin uygunluğunu kılavuzlar eşliğinde değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya Aralık 2022 ve Ocak 2023 tarihleri arasında İstanbul ilinde aile sağlığı merkezlerinde görev yapan aile hekimliği uzmanları, aile hekimi olarak görev yapan pratisyen hekimler, ikinci ve üçüncü basamak hastanelerde görev alan aile hekimliği uzmanı ve asistanları dahil edilmiştir. Veri toplama amacıyla Google Formu oluşturularak online olarak bu formlar hekimlere ulaştırılmıştır.

Bulgular: Çalışmaya 421 hekim dahil edilmiştir. Fosfomisin, nitofurantoin, sefalosporin, sulfonamid, florokinolonon (FQ) ve penisilin için kullanım oranları sırasıyla; %83,8 (n=353), %52,3 (n=220), %24 (n=101), %14,5 (n=61), %26,6'sı (n=112), %10,7 (n=45) bulunmuştur. FQ ve aminopenisilinlerin non-komplike sistitin birinci basamak tedavisinde kullanımlarının olmadığı kabul edildiğinde, yaşça daha küçük ve görev süresi kısa olan hekimlerde doğru ampirik antibiyotik reçete etme oranı daha yüksektir (p=0,001). Ayrıca aile hekimliği yapan pratisyen doktorlar, aile hekimi uzmanı ve asistanlarına göre anlamlı olarak daha yüksek oranda yanlış ampirik tedavi uygulamışlardır (%39,3 vs. %10 ve %11,9).

Address for Correspondence: Deniz Noyan Özlü, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Urology, İstanbul, Türkiye
Phone: +90 535 233 64 40 E-mail: noyanozlu@hotmail.com ORCID ID: orcid.org/0000-0003-2435-5482

Cite as: Polat H, Özlü DN. Appropriateness of the Empirical Antibiotherapy Choices of Primary Care Physicians for the Treatment of Uncomplicated Cystitis. Med J Bakirkoy 2023;19:308-313

Received: 18.08.2023
Accepted: 05.09.2023

Sonuç: Birinci basamak sağlık hizmeti veren hekimlerimizin önemli bir kısmı halen rehberlerde önerilmeyen antibiyotikleri non-komplike sistitte ampirik tedavide reçete etmektedirler. Pratisyen hekimlerin ve yaşça büyük hekimlerin ampirik tedavide daha yüksek oranda yanlış tedavi seçimleri bize birinci basamak sağlık hizmetlerinde hizmet içi eğitim ihtiyacını göstermektedir.

Anahtar Kelimeler: Birinci basamak sağlık hizmetleri, sistit, idrar yolu enfeksiyonu, antibakteriyel ajanlar

INTRODUCTION

Uncomplicated cystitis is defined as acute, sporadic, or recurrent cystitis that is limited to non-pregnant women without comorbidities or known anatomical and functional abnormalities in the urinary tract (1). One in every three women experiences at least one episode of cystitis before the age of 24 (2). The most important cause of uncomplicated cystitis is *Escherichia coli* (*E. coli*). The presence of symptoms of the lower urinary system, such as dysuria, frequency, and urgency, together with supporting anamnesis, is sufficient for the diagnosis of this condition (1).

In primary healthcare services, the frequency of inappropriate antibiotic prescriptions for urinary tract infections (UTIs) is very high, with fluoroquinolone (FQ) being one of the leading inappropriate choices (3). The resistance of common UTI pathogens to FQ and trimethoprim-sulfamethoxazole (TMP-SMX) is increasing every year, and the prevalence of extended-spectrum beta-lactamase and other multidrug resistance is also increasing (4,5). It has been stated that the use of antibiotics only when needed should be a standard approach to reduce adverse drug effects and antibiotic resistance (6). Given the negative effects of inappropriate antibiotic use on individuals and societies, physicians should select appropriate antibiotic therapy for managing UTIs. In addition, healthcare professionals should be aware of local antibiotic resistance (6).

In this study, we aimed to evaluate the appropriateness of antibiotic choices of primary care physicians for treating adult patients with uncomplicated cystitis considering relevant international guidelines.

METHODS

Family physicians working in family health centers (FHCs), general practitioners working as family physicians, and family medicine specialists and assistants working in secondary and tertiary care hospitals in İstanbul between December 2022 and January 2023 were included in the study. A Google form was created for data collection and was distributed to physicians online. An invitation to participate in the study was sent to all participants via e-mail on December 1, 2022. Before completing the survey, all participants were directed to an informed consent page, and only those who agreed to participate in the study were able to access the form. The responses given until January 31, 2022 were recorded. Forms with missing responses were invalid and excluded.

The age, gender, title (general practitioner, assistant, or specialist), center, and professional experience of the participants were determined using the survey. Another question in the survey was related to which cases of UTIs the physicians would request a urinalysis for and whether this would be accompanied by urine culture. The patient profile, which was created to direct physicians to the preliminary diagnosis of uncomplicated cystitis, was planned as a healthy, non-pregnant female patient, and the empirical antibiotic choices of the participants were questioned by allowing more than one response. In accordance with the European Association of Urology (EAU) Urological Infections Guidelines (1) and the Infectious Diseases Society of America (IDSA) (7) guidelines, physicians who included FQ and/or aminopenicillin in their empirical antibiotic prescriptions had inappropriate treatment choices, and the rates of inappropriate antibiotic use were compared according to the demographic data of the physicians.

The methodology of the study and the survey were approved by the Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2023-01-18, date: 09.01.2023).

Statistical Analysis

Frequency and rates were used as descriptive statistics. The chi-square test was conducted to analyze qualitative, independent data. The SPSS v. 28.0 software package was used for statistical analysis.

RESULTS

A total of 421 physicians participated in the study. Demographic data on the participating physicians are given in Table 1. Accordingly, 37.8% (n=159) of the physicians were <30 years old, 35.6% (n=150) were 30-40 years old, 19% (n=80) were 40-50 years old, and 7.6% (n=32) were >50 years old. Of the entire physician group, 54.9% (n=231) were men and 45.1% (n=190) were women.

The rate of family medicine assistants was 25.9% (n=109), and that of family medicine specialists was 14.3% (n=60).

The rate of general practitioners working as family physicians was found to be 59.9% (n=252). When the centers at which the participants worked were examined, it was determined that 62.2% (n=262) physicians worked in FHCs, while 37.8% (n=159) worked in secondary or tertiary hospitals.

Regarding the question, "In which cases would you request a urinalysis?", the physicians were able to select more than one option (Table 2). The 'yes' response was recorded at the following rates: presence of systemic symptoms, 96.9% (n=408); pregnancy, 92.2% (n=388); presence of a urinary tract catheter, 60.6% (n=255); presence of a concomitant chronic disease, 32.5% (n=137); and older age, 27.6% (n=116). In addition, 6.2% (n=26) of the physicians stated that they would request a urine culture in addition to urinalysis.

The physicians were presented with a patient profile that suggested uncomplicated cystitis and were asked which empiric antibiotic they would prefer for treating such a patient. They could select more than one option. For empirical treatment, most physicians chose fosfomycin (83.8%, n=353), followed by nitrofurantoin (52.3%, n=220), cephalosporins (24%, n=101), and sulfonamides (14.5%, n=61). In addition, 26.6% (n=112) of the physicians stated that they would use FQ, and 10.7% (n=45) stated that they would use penicillin in the empirical treatment of UTIs.

Table 1. Demographic data of physicians

	n (%)	
Age	<30 years	159 (37.8)
	30-40 years	150 (35.6)
	40-50 years	80 (19.0)
	>50 years	32 (7.6)
Gender	Male	231 (54.9)
	Female	190 (45.1)
Title	Specialist	60 (14.3)
	Assistant	109 (25.9)
	Practitioner	252 (59.9)
Center	Family health center	262 (62.2)
	Hospital	159 (37.8)
Tenure	<10 years	194 (46.1)
	10-20 years	142 (33.7)
	20-30 years	63 (15.0)
	>30 years	21 (5.0)
Empirical treatment choice	Appropriate	278 (66.0)
	Inappropriate	142 (33.7)

Quinolones and aminopenicillins should not be used in the first-line treatment of uncomplicated cystitis, and physicians who selected at least one of these antibiotics were considered to have inappropriate empirical treatment choices. When the rates of inappropriate responses were compared according to the age, gender, title, and tenure of the participants (Table 3), they did not significantly differ between male and female physicians (p=0.348); however, there were statistically significant differences according to age and tenure. Younger physicians and those with shorter tenure had statistically significantly higher rates of appropriate empirical treatment choices than older physicians and those with longer tenure, respectively (p=0.001). In addition, general practitioners working as family physicians had inappropriate empirical treatment choices at a significantly higher rate than family medicine specialists and assistants (39.3% vs. 10% and 11.9%, p=0.002).

DISCUSSION

Although the need for antibiotics for treating symptomatic UTIs is clear, the most important decision concerns antibiotic selection and optimization of treatment duration (3). Another question is whether urinalysis or urine culture should be requested in addition to the initiation of empirical antibiotherapy. In patients presenting with the typical symptoms of uncomplicated cystitis, urinalysis may lead to only a minimal increase in diagnostic accuracy (8).

Table 2. Survey questions and distribution of physicians' responses

In which cases would you request urinalysis?	Systemic symptoms (sweating with fever, fatigue, nausea, and vomiting, etc.)	408 (96.9%)
	Pregnancy	388 (92.2%)
	Urinary catheter	255 (60.6%)
	Concomitant chronic disease	137 (32.5%)
	Older age	116 (27.6%)
Would you like to request urine culture with urinalysis?	Yes	26 (6.2%)
	No	395 (93.8%)
A healthy, non-pregnant female patient presented with a urinary tract infection. What would be your empirical antibiotic choice?	Fosfomycin	353 (83.8%)
	Nitrofurantoin	220 (52.3%)
	Quinolinone	112 (26.6%)
	Cephalosporin	101 (24%)
	Sulfonamide	61 (14.5%)
	Penicillin	45 (10.7%)
	Other	30 (7.1%)

Table 3. Comparative analysis of appropriate response rates according to physicians' demographic data

n (%)		Appropriate antibiotic choice	Inappropriate antibiotic choice	p-value
		n (%)		
Age	<30 years	122 (76.7)	37 (23.3)	**0.001**[X²]
	30-40 years	86 (57.3)	64 (42.7)	
	40-50 years	53 (66.3)	27 (33.8)	
	>50 years	17 (53.1)	15 (46.9)	
Gender	Male	148 (64.1)	83 (35.9)	0.348[X²]
	Female	130 (68.4)	60 (31.6)	
Title	Specialist	54 (90)	6 (10)	**0.002**[X²]
	Assistant	96 (88.1)	13 (11.9)	
	Practitioner	153 (60.7)	99 (39.3)	
Center	Family health center	180 (68.7)	82 (31.3)	0.138[X²]
	Hospital	98 (61.6)	61 (38.4)	
Tenure	<10 years	144 (74.2)	50 (25.8)	**0.001**[X²]
	10-20 years	93 (65.5)	49 (34.5)	
	20-30 years	35 (55.6)	28 (44.4)	
	>30 years	6 (28.6)	15 (71.4)	

[X²]Chi-square test

The EUA guidelines indicate the use of the urine dipstick test at a 'weak' recommendation level in the diagnosis of uncomplicated cystitis and state that urine culture should only be used in the presence of suspected pyelonephritis, symptoms that persist despite the completion of treatment or recur within four weeks, atypical symptoms, or pregnancy (1). In a study conducted to increase diagnostic accuracy and reduce unnecessary antibiotic use in women with suspected cystitis, the factors associated with a positive urine culture were dysuria, positivity in urinalysis, and the presence of more than trace amounts of leukocytes (9). Almost all the physicians who participated in our study stated that they would request a urinalysis in the presence of systemic symptoms, such as fever, sweating, fatigue, nausea, vomiting (96.9%), and pregnancy (92.2%). Although there is no guideline recommendation related to older age, the presence of a urinary catheter, or comorbidities, we determined that a urinalysis would be requested in these cases by 60.6%, 32.5%, and 27.6% of the physicians, respectively. Lastly, the rate of those who requested a urine culture with a urinalysis was determined to be only 6.2%.

In the empirical treatment of uncomplicated cystitis, the EAU guidelines recommend a single 3 g dose of fosfomycin, 3x400 mg of pivmecillinam for three to five days (not available in Türkiye), or 2x100 mg of nitrofurantoin for five days. As an alternative, cephalosporins or TMP-SMX can be administered if the resistance pattern is suitable (1). Similarly, in the IDSA guidelines, single-dose fosfomycin, five-day nitrofurantoin, and TMP-SMX are recommended as appropriate antibiotherapy options for uncomplicated cystitis in adults, whereas ciprofloxacin, levofloxacin, and TMP-SMX are presented as the first-line treatment options for pyelonephritis (6,7,10).

Nitrofurantoin is an old antibiotic that specifically targets the urinary tract and has bacteriostatic effects at low concentrations and bactericidal effects at high concentrations (11). In a study conducted by Grigoryan et al. (12) in the USA, nitrofurantoin was found to be the second most frequently used antibiotic for treating uncomplicated cystitis in primary healthcare services. In the same study, other mostly prescribed antibiotics were determined to be FQ and TMP-SMX, and it was reported that the treatment durations were longer than recommended by the guidelines. Older age and the presence of diabetes were found to be the most important predictors of a treatment duration longer than necessary (12). Although nitrofurantoin is recommended as the first-line treatment option by the EAU and IDSA guidelines, which were used as reference standards in our study, we determined a rate of 52.3% for nitrofurantoin preference among physicians in the empirical treatment of uncomplicated cystitis.

Although fosfomycin has been used for many years in Türkiye, its resistance rates are very low. Fosfomycin is a phosphoenolpyruvate analog and a fermentation product of *Streptomyces viridochromogenes*, *Streptomyces fradiae*, and *Streptomyces wedmorensis* (11). Grigoryan et al. (12) reported that fosfomycin was not preferred by primary care physicians. We observed that 83.8% of the physicians preferred fosfomycin in the empirical treatment of uncomplicated cystitis, as recommended by both the EAU and IDSA guidelines.

The EAU guidelines do not indicate the use of FQ or aminopenicillins at a 'strong' recommendation level in uncomplicated cystitis (1). In addition to FQ being known to cause serious adverse effects, their use in cystitis increases antibiotic resistance and paves the way for *Clostridium difficile* infections (6,13). The aminopenicillin resistance of *E. coli* is very common, and the probability of treatment failure with this agent is very high (1,7). Similarly, the IDSA guidelines exclude beta-lactams as a suitable option for

the treatment of UTIs because of their low efficacy and the availability of many other antibiotic options for adults with appropriate local sensitivities (6,7). In our study, 26.6% of the physicians preferred FQ and 10.7% preferred penicillin in the empirical treatment of uncomplicated cystitis.

In 2019, the European Medicine Agency took a decision that would be valid in all European Union countries, introducing limitations based on the rational use of FQ to minimize its potential side effects (14). In uncomplicated cystitis, FQ should be used only if other common agents are not appropriate. In a recent study conducted in the USA, it was observed that the most commonly prescribed antibiotic in uncomplicated UTIs was FQ, which is recommended to be used not in first-line treatment but in more serious infections, and that it constituted half of all prescriptions (12,15). FQ is still highly preferred in primary care medicine, despite the resistance of *E. coli* to this agent being 20% in the USA, and this rate is almost ten times that reported for fosfomycin (1-2%) (4).

In a recent study, Chardavoyne and Kasmire (6) examined the antibiotics prescribed for the treatment of UTIs in emergency departments. Similar to our study, they used the IDSA guidelines and UpToDate as a reference for appropriate antibiotic therapy in adult women (6,10). They determined that amoxicillin and beta-lactams constituted 79% of inappropriate antibiotics prescribed for UTIs. In addition, FQ prescribed for cystitis constituted 6% of inappropriate prescriptions, and nitrofurantoin administered for pyelonephritis constituted 12% of inappropriate antibiotic use (6). In the same study, it was also emphasized that the use of antibiotics for longer than recommended contributed to antibiotic resistance, and the rate of antibiotic prescription at the correct dose and duration in adults with uncomplicated cystitis was only 34%.

In the literature, studies of European origin examining compliance with the relevant UTI guidelines have yielded different results. In a study conducted in France, it was observed that only 20% of outpatients presenting with UTIs were treated with the agent, dose, and duration recommended by the guidelines (16). While the rate of use of first-line antibiotics in the empirical treatment of uncomplicated UTI was reported to be 18% in Spain (17), compliance with the guidelines in antibiotic selection was very high in Norway, with the rate of FQ preference being only 6% (18). In a 2014 study covering six European countries, TMP-SMX was the most preferred antibiotic for lower UTIs, whereas the rate of complete treatment compliance was reported to be 72.7% in the Netherlands, 40% in Denmark, 38.3% in Norway, and 22.2% in Slovenia (19). In the current study, sulfonamides were preferred at a rate of 14.5% as the first-line treatment.

In addition to the guideline recommendations on the management of uncomplicated cystitis, knowing the antibiotic resistance profile in Türkiye has an important place in treatment planning. In a large-scale study on this subject, the resistance rates of TMP-SMX, amoxicillin-clavulanate, and FQ among outpatients were found to be 47.1%, 31.5%, and 20.1%, respectively (20). In another study conducted in the pediatric patient group, the antibiotics with the highest resistance in all Gram-negative microorganisms obtained from the urinary tract were as follows: ampicillin (75.1%), cefazolin (59%), ampicillin-subactam (49.7%), ceftriaxone (31.4%), cefixime (33.1%), and TMP-SMX (45.2%). The lowest resistance was found in meropenem (3.2%), whereas other antibiotics with low resistance rates were ertapenem (3.4%), colistin (7.2%), amikacin (16.2%), and ciprofloxacin (21.1%) (21). The authors stated that they found ciprofloxacin resistance to be higher than previously reported. In a more recent study, isolates were examined in urine culture, and the resistance rates were determined to be 81% for ampicillin, 42% for amoxicillin-clavulanic acid, 42% for cefixime, 41% for ciprofloxacin, 40% for TMP-SMX, 18% for gentamicin, 5% for amikacin, 4% for nitrofurantoin, 4% for fosfomycin, and 2% for imipenem (2%) (22). Here, TMP-SMX, which is recommended by the guidelines for first-line treatment, shows a very high resistance pattern in Türkiye. However, it was observed that nitrofurantoin and fosfomycin still have high efficacy.

Our results show that, in primary care, compliance with the relevant guidelines is low in antibiotherapy agent selection for treating uncomplicated cystitis, and there is a need to develop focused strategies to increase this compliance. The ideal antibiotic therapy plan should be determined based on the current local prevalence of resistance to common uropathogens, not merely on drug tolerability. The higher rate of appropriate treatment preferences among younger physicians with shorter tenure and the higher preference for inappropriate antibiotic regimens among general practitioners indicate the need for in-service training in terms of rational antibiotic use. The most important shortcoming of our study is that the participants were limited to family physicians in İstanbul, and therefore, the results cannot be generalized to the whole of Türkiye, considering the sample size. In addition, because the data collection tool used in the study was a survey, the physicians' responses may not reflect their actual preferences in clinical practice or the real situation in the field.

CONCLUSION

A significant portion of the primary care physicians who participated in this study were found to prefer antibiotics that are not recommended in the relevant guidelines and are even considered objectionable due to their side-effect profile and resistance patterns in the empirical treatment of uncomplicated cystitis. The higher rates of inappropriate empirical treatment choices by general practitioners and senior physicians indicate that the approach to uncomplicated cystitis in primary healthcare services should be improved with in-service training.

ETHICS

Ethics Committee Approval: The methodology of the study and the survey were approved by the Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2023-01-18, date: 09.01.2023).

Informed Consent: Before completing the survey, all participants were directed to an informed consent page, and only those who agreed to participate in the study were able to access the form.

Authorship Contributions

Surgical and Medical Practices: H.P., Concept: H.P., Design: H.P., D.N.Ö., Data Collection or Processing: H.P., Analysis or Interpretation: D.N.Ö., Literature Search: H.P., D.N.Ö., Writing: H.P., D.N.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam, the Netherlands [internet] 2022. Accessed on: 05/03/2023 Available from https://uroweb.org/guidelines/urological-infections/chapter/the-guideline.
2. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med 2002;113:5-13.
3. Grigoryan L, Zoorob R, Germanos G, Sidani M, Horsfield M, Khan F, et al. Case-based audit and feedback around a decision aid improved antibiotic choice and duration for uncomplicated cystitis in primary care clinics. Fam Med Community Health 2021;9:e000834.
4. Sanchez GV, Babiker A, Master RN, Luu T, Mathur A, Bordon J. Antibiotic Resistance among Urinary Isolates from Female Outpatients in the United States in 2003 and 2012. Antimicrob Agents Chemother 2016;60:2680-3.
5. Bidell MR, Palchak M, Mohr J, Lodise TP. Fluoroquinolone and Third-Generation-Cephalosporin Resistance among Hospitalized Patients with Urinary Tract Infections Due to Escherichia coli: Do Rates Vary by Hospital Characteristics and Geographic Region? Antimicrob Agents Chemother 2016;60:3170-3.
6. Chardavoyne PC, Kasmire KE. Appropriateness of Antibiotic Prescriptions for Urinary Tract Infections. West J Emerg Med 2020;21:633-9.
7. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.
8. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? JAMA 2002;287:2701-10.
9. Mclsaac WJ, Moineddin R, Ross S. Validation of a decision aid to assist physicians in reducing unnecessary antibiotic drug use for acute cystitis. Arch Intern Med 2007;167:2201-6.
10. Hooton TM, Gupta K. Acute simple cystitis in women. Post TW, editor. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com.
11. Taşbakan MI. Urinary tract infections and rational use of antibiotics. Ankem Derg 2014;28:178-81.
12. Grigoryan L, Zoorob R, Wang H, Trautner BW. Low Concordance With Guidelines for Treatment of Acute Cystitis in Primary Care. Open Forum Infect Dis 2015;2:ofv159.
13. Food and Drug Administration. Fluoroquinolone antimicrobial drugs information. [internet] Available from https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass.htm..
14. European Medicines Agency. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. Quinolone and fluoroquinolone Article-31 referral, [internet] 2019. Available from https://www.ema.europa.eu/en/ documents/referral/quinolone-fluoroquinolone-article-31-referraldisabling- potentially-permanent-side-effects-lead_en.pdf
15. Kobayashi M, Shapiro DJ, Hersh AL, Sanchez GV, Hicks LA. Outpatient Antibiotic Prescribing Practices for Uncomplicated Urinary Tract Infection in Women in the United States, 2002-2011. Open Forum Infect Dis 2016;3:ofw159.
16. Denes E, Prouzergue J, Ducroix-Roubertou S, Aupetit C, Weinbreck P. Antibiotic prescription by general practitioners for urinary tract infections in outpatients. Eur J Clin Microbiol Infect Dis 2012;31:3079-83.
17. Llor C, Rabanaque G, López A, Cots JM. The adherence of GPs to guidelines for the diagnosis and treatment of lower urinary tract infections in women is poor. Fam Pract 2011;28:294-9.
18. Agdestein B, Lindbæk M, Gjelstad S. Do general practitioners follow the national guidelines for treating urinary tract infections with antibiotics?. Tidsskr Nor Laegeforen 2011;131:1641-4.
19. Philips H, Huibers L, Holm Hansen E, Bondo Christensen M, Leutgeb R, Klemenc-Ketis Z, et al. Guidelines adherence to lower urinary tract infection treatment in out-of-hours primary care in European countries. Qual Prim Care 2014;22:221-31.
20. Aykan SB, Ciftci IH. Türkiye'de İdrar Kültürlerinden İzole Edilen Escherichia coli Suşlarının Antibiyotiklere Direnç Durumu: Bir Meta-Analiz [Antibiotic resistance patterns of Escherichia coli strains isolated from urine cultures in Turkey: a meta-analysis]. Mikrobiyol Bul 2013;47:603-18.
21. Kömürlüoğlu A, Aykaç K, Özsürekçi Y, Başaranoğlu ST, Bıçakçıgil A, Liste Ü, et al. [Antibiotic Resistance Distribution of Gram-Negative Urinary Tract Infection Factors: A Single Center Experience.] Türkiye Çocuk Hast Derg 2018;12:10-7.
22. Avcıoğlu F, Behçet M. [Evaluation of Resistance Rates of Escherichia coli Isolates of Urinary Tract Infection to Various Antibiotics] Turk Mikrobiyol Cemiy Derg 2020;50:172-7.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:314-318
DOI: 10.4274/BMJ.galenos.2023.2023.8-7

Research

Evaluation of the Effectiveness of Transversus Abdominis Plane Block and Transversalis Fascia Plane Block in Postoperative Analgesia in Pediatric Patients Undergoing Lower Abdominal and Genitourinary Surgery: A Retrospective Study

Alt Abdominal ve Genitoüriner Cerrahi Geçiren Pediatrik Hastalarda Postoperatif Analjezide Transversus Abdominis Plane Bloğu ve Transversalis Fascia Plane Bloğunun Etkinliğinin Değerlendirilmesi: Retrospektif Çalışma

Necmiye Ay, Duygu Akyol, Funda Gümüş Özcan

University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Türkiye

ABSTRACT

Objective: Peripheral trunk blocks are used for multimodal analgesia in pediatric ambulatory surgery. In this study, we aimed to evaluate the efficacy of transversus abdominis plane block (TAPB) and transversalis fascia plane block (TFPB) for postoperative acute analgesia in lower abdominal and urogenital surgeries in pediatric patients.

Methods: In our study, patients aged 3-16 years, American Society of Anesthesiology I-III, who underwent lower abdominal-urogenital surgery and peripheral trunk blocks for postoperative analgesia were retrospectively reviewed. Pain scores in the first 6 hours (h) postoperatively, additional analgesia needs of patients, and complications were evaluated.

Results: Ninety-five patients who underwent TAPB and transversalis fascia plane block were evaluated. There was no statistically significant difference between the demographic data and operation time. The number of patients with a pain score >4 in the first 6 h was higher in the TAPB group ($p<0.05$). The additional analgesic requirement was lower in the TFPB group ($p<0.05$). There were no postoperative complications in either group.

Conclusion: Peripheral trunk blocks can be used as a part of multimodal analgesia for early postoperative discharge in pediatric surgeries.

Keywords: Peripheral trunk block, postoperative analgesia, pediatric ambulatory surgery

ÖZ

Amaç: Pediatrik günübirlik cerrahilerde multimodal analjezi amacıyla periferik gövde blokları kullanılmaktadır. Biz de çalışmamızda pediatrik hastaların alt batın ve ürogenital cerrahilerinde uygulanan transversus abdominis plane bloğu (TAPB) ile transversalis fascia plane (TFPB) bloğunun postoperatif akut dönemde analjezide etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmamızda 3-16 yaş arası, Amerikan Anesteziyoloji Derneği I-III, alt batın-ürogenital cerrahi geçiren ve postoperatif analjezi amacıyla periferik gövde blokları uygulanan hastalar retrospektif olarak incelendi. Postoperatif ilk 6 saatteki (s) ağrı skorları, hastaların ek analjezi ihtiyaçları ve komplikasyonlar değerlendirildi.

Bulgular: TAPB ve TFPB uygulanan 95 hasta değerlendirildi. Demografik verileri ve operasyon süreleri arasında istatistiksel anlamlı farklılık görülmedi. İlk 6 s'de ağrı skoru >4 olan hasta sayısı TAPB grubunda daha fazlaydı ($p<0,05$). Ek analjezik ihtiyacı TFPB grubunda daha düşüktü ($p<0,05$). Her iki grupta da postoperatif komplikasyon görülmedi.

Address for Correspondence: Necmiye Ay, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Türkiye
Phone: +90 212 909 60 00 E-mail: hisarneco@hotmail.com ORCID ID: orcid.org/0000-0003-1787-7522

Cite as: Ay N, Akyol D, Gümüş Özcan F. Evaluation of the Effectiveness of Transversus Abdominis Plane Block and Transversalis Fascia Plane Block in Postoperative Analgesia in Pediatric Patients Undergoing Lower Abdominal and Genitourinary Surgery: A Retrospective Study. Med J Bakirkoy 2023;19:314-318

Received: 23.08.2023
Accepted: 14.09.2023

Sonuç: Pediatrik günübirlik cerrahilerde erken taburculuk amacıyla multimodal analjezinin bir parçası olarak periferik gövde blokları kullanılabilir.
Anahtar Kelimeler: Periferik gövde blokları, postoperatif analjezi, pediatrik günübirlik cerrahi

INTRODUCTION

A multimodal approach, including pharmacological agents and neuraxial and peripheral nerve blocks, should be used to reduce postoperative pain in pediatric surgeries (1). Although the caudal block is the gold standard, trunk blocks as part of multimodal analgesia have gained popularity in pediatric patients because of their more prolonged efficacy, less invasiveness, and lower complication rates (2). These blocks are preferred more frequently with the widespread use of ultrasonography (USG) (3). Transversus abdominis plane block (TAPB) and transversal fascia plane block (TFPB) may be preferred, especially in lower abdomen urogenital surgeries. TAPB is a block applied to the anatomical neurofascial space between the internal oblique and transversus abdominis muscle located in the anterolateral region of the abdomen, targeting the anterior branches of the T6-12 and L1 nerves (4,5). The transversalis fascia plan block is a newer block than the TAPB and is a posterior abdominal plan block targeting the T12 and L1 nerves between the transversus abdominis muscle and transversalis fascia (6). These blocks reduce the need for postoperative analgesia. TAPB is effective in open inguinal hernia operations in pediatric patients (5). TFPB also provides effective analgesia in the postoperative period after pediatric inguinal hernia operations and reduces postoperative anesthetic consumption (7). Thus, patient comfort is increased with effective analgesia and early mobilization and discharge (1,8). In particular, in pediatric ambulatory surgery patients, postoperative pain management is inadequate in most centers, and a multifaceted approach is required in pain management (1).

In our study, we compared the postoperative analgesic efficacy of TAPB and TFPB in pediatric patients undergoing lower abdominourogenital surgery.

METHODS

Our study was planned retrospectively on the basis of the Declaration of Helsinki principles, after University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Ethics Committee approval (decision no: 252 date: 27.07.2022). Between 01.01.2022 and 01.06.2022, the files of patients aged 3-16 years, American Society of Anesthesiology (ASA) I-III class, who underwent lower abdominal and urogenital (undescended testis, inguinal hernia, appendectomy, hydrocele, testicular torsion) surgery under general anesthesia were reviewed. Pediatric patients who underwent TAPB or TFPB for postoperative analgesia were included in this study. Our study included 95 patients, as part of the TFPB group in patients who underwent TFPB and the TAPB group in patients who underwent TAPB. One hundred ten patients were evaluated in the study. Fifteen patients whose duration of operation was below 30 min were excluded, and 95 patients were divided into two groups as TAPB and TFPB (Figure 1). Preoperative demographic data, such as age, weight, and comorbidity, along with the ASA scores were also recorded.

All patients with open vascular access received lidocaine (1 mg/kg), fentanyl (1 mcg/kg), and propofol (2.5-3 mg/kg) for the induction of anesthesia. 0.6 mg/kg rocuronium was administered to patients who were intubated orotracheally, and if necessary, 0.2 mg/kg rocuronium was administered to patients who were ventilated with a laryngeal mask. Anesthesia induction was performed using sevoflurane in patients without intravenous access. Anesthesia induction was performed with sevofluorane in patients without intravenous access. 10 mg/kg paracetamol was used intravenously for analgesia during surgery. TAPB or TFPB (0.5 mL/kg of 0.25% bupivacaine) was performed for postoperative analgesia with in plane technique under USG guidance while under general anesthesia at the end of surgery. After the block, anesthesia maintenance was terminated, sugammadex (3-5 mg/kg) was administered,

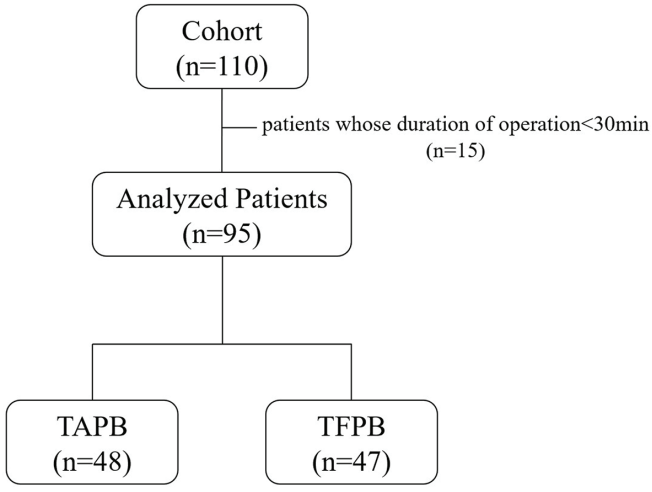

Figure 1. Consort flow diagram of study
TAPB: Transversus abdominis plane block, TFPB: Transversalis fascia plane block

and the patients were extubated when adequate respiration was achieved. Patients were followed up in the recovery room for 30 min after surgery. Patients with a modified aldrete score >9 were transferred from the recovery unit to the ward. In our hospital, pain scores (PS) of patients operated on in pediatric surgery are routinely measured when the patients are awakened and taken to the recovery unit (T1), at the 30th minute (T2) in the recovery unit, and at the 6th hour (h) (T3) in the ward, and these scores are recorded. The Faces, Legs, Activity, Cry, and Consolability for 0-5 year-olds; Modified Objective PS for 6-11-year-olds; and visual PS for those older than 12 years were used. If the PS was >4 according to these scores, 10 mg/kg paracetamol was administered iv. The need for additional analgesia and the presence of nausea and vomiting were recorded.

Demographic data, ASA scores, PSs at T1, T2, and T3, and postoperative complications were obtained from the documents and recorded. The primary outcome in the study was the number of patients with PS >4 in the first 6 h after surgery.

Statistical Analysis

In the analysis of the data, we used SPSS 20 for Windows (IBM Corp., Armonk, NY, USA), and the Kolmogorov-Smirnov test was used to evaluate the normal distribution of the data. The normally distributed variables are presented as the mean ± standard deviation, whereas the non-normally distributed variables are presented as the median (interquartile range: 25-75 percentiles). Categorical variables are presented as numbers and percentages. For the group comparison of normally distributed variables, Student's t-test and Mann-Whitney U tests were used for the intergroup comparison of non-normally distributed variables. For the intergroup comparison of the categorical variables, the chi-square and Fisher Exact tests were used. For the consideration of the statistically significant value, $p<0.05$ was accepted.

The estimated power of this study was 0.90 for the percentage of the number of patients with PS >4 in the first 6 h (for total patients in groups: 48 and 47, and for percentages of groups: 35.4% and 8.5%).

RESULTS

A total of 95 pediatric patients undergoing lower abdominal and urogenital surgery under general anesthesia were divided into two groups TFPB (n=47) and TAPB (n=48) (Figure 1). The median ages of patients for TAPB and TFPB were 7 and 6 years old respectively (Table 1). Among the surgical cases, inguinal hernia rates were the highest in both groups, although not statistically significant. The operation times were similar in both groups ($p>0.05$) (Table 1).

The postoperative pain scores and complications are shown in Table 2. The two groups showed no statistically significant difference when pain scores were evaluated at T2 and T3. At the T1 time point, the median pain score was lower in the TFPB group ($p<0.05$). The pain scores and additional analgesic requirements in the first 6 h were both higher in the TAPB group ($p<0.05$). There were no postoperative complications in either group (Table 2).

Table 1. Patients' and operations' characteristics

	TAPB (n=48)	TFPB (n=47)	p-value
Age, years	7 (4-13)	6 (4-9)	0.478
<5 years old	23 (47.9)	22 (46.8)	0.231
>6 and <12 years old	11 (22.9)	17 (36.2)	
≥12 years old	14 (29.2)	8 (17.0)	
Weight, kg	23 (17-44)	22 (17-38)	0.698
ASA	1 (1-1)	1 (1-1)	0.088
Duration of operation, hours	50 (40-59)	55 (40-60)	0.458
Surgical diagnosis, n (%)			
Inguinal hernia	31 (64.6)	23 (48.9)	0.234
Undescended testicle	6 (12.5)	12 (25.4)	
Appendectomy	5 (10.4)	3 (6.4)	
Hydrocele	5 (10.4)	5 (10.6)	
Testicular torsion	1 (2.1)	4 (8.5)	

ASA: American Society of Anesthesiology, TAPB: Transversus abdominis plane block, TFPB: Transversalis fascia plane block

Table 2. Comparison between postoperative pain scores of groups

	TAPB (n=48)	TFPB (n=47)	p-value
PS			
At the T1	1 (0-3)	0 (0-2)	**0.033**
At the T2	2 (0-5)	2 (0-3)	0.212
At the T3	2 (0-5)	1 (0-2)	0.069
PS-max in the first 6 h	3 (1-5)	2 (0-4)	**0.022**
The number of patients with PS >4 in the first 6 h, n (%)	17 (35.4)	4 (8.5)	**0.002**
Additional analgesic requirements, n (%)	19 (39.6)	4 (8.5)	**>0.001**
Complications, n (%)	0 (0.0)	0 (0.0)	NS

PS: Pain score, TAPB: Transversus abdominis plane block, TFPB: Transversalis fascia plane block

DISCUSSION

The aim of this retrospective study was to evaluate the efficacy of TFPB and TAPB in reducing postoperative acute pain scores in pediatric patients who underwent lower abdominal and urogenital surgery. Pain scores at first evaluation (T1) were significantly lower in the TFPB group compared to TAPB. The number of patients with pain scores >4 and additional analgesic requirements in the first 6 h was lower in the TFPB group ($p<0.05$).

Ambulatory surgery is becoming increasingly common in pediatric patients. Reduction of pain in patients is important before discharge (1,9). Studies have shown that blocks are an effective method for relieving postoperative pain and reducing the use of opioid analgesics. In particular, when combined with a multimodal technique, trunk blocks provide adequate analgesia in patients undergoing day surgery (1,8). Thus, the duration of hospitalization, risk of nosocomial infection, and healthcare costs are reduced with effective analgesia (1,10).

The incision in the abdominal wall causes parietal pain in inguinal hernia surgery. TAPB aims to block the neurofascial nerves between the internal oblique and transversus abdominis muscles along the TAP (4). In children undergoing elective inguinal hernia surgery, USG-guided TAPB has been shown to provide longer postoperative analgesia, have fewer side effects, and reduce the need for rescue analgesics compared with caudal block, which is considered the gold standard in analgesia (2,11). Abu Elyazed et al. (5) showed that TAPB, a part of multimodal analgesia, provides effective analgesia in pediatric inguinal hernia repair. In appendectomy cases in pediatric patients, it was shown that postoperative pain scores were lower in the group in which the TAPB was applied than in the control group (12). In another study, a TAPB applied in inguinal hernia operations in pediatric patients aged 4-7 years was more effective than wound site local anesthetic infiltration (13). In the TFPB, one of the trunk blocks, the nerves between the lumbar plexus and TAPB are targeted with a local anesthetic injected between the transversus abdominis muscle and its deeply folded transversalis fascia (5). TFPB has also been reported to provide effective postoperative analgesia in lower abdominal surgery in pediatric patients (14). Abdelbaser et al. (7) showed that TFPB contributed to postoperative analgesia in inguinal hernia cases in pediatric patients aged 1-5 years compared with the control group. Peksöz et al. (15) applied a TFPB for postoperative analgesia in 5 pediatric patients aged 4-7 who underwent ureteroneocystostomy. When pain scores were evaluated for 24 h postoperatively, they were shown to be below 4 and effective in analgesia (15).

López-González et al. (16) compared the efficacy of TFPB and TAPB for postoperative analgesia in patients undergoing unilateral inguinal herniorrhaphy. It has been shown that a higher sensory level was reached in patients who underwent TFPB; however, there was no difference in the need for additional analgesia (16). Because the patients were evaluated retrospectively, only pain assessments up to the 6th h were performed. Because it was a day surgery, 24 h analgesic requirement and pain assessment could not be performed. Our study showed that the number of patients with a maximum pain score of >4 in the first 6 h was found to be significantly less in the TFP group. No side effects were reported in our patients with both blocks, and the discharge of patients was not delayed.

TFPB, which is a newer method in this study, provides better analgesia than TFP. We believe that the similarity of pain scores at 30 min and 6 h was achieved with additional analgesics administered in the TAP group.

CONCLUSION

Outpatient surgery is becoming increasingly common in pediatric patients and affects the duration of discharge when pain management is inadequate. As a result of our findings, TFPB, a newer method, seems to be more effective than TAPB in pediatric patients undergoing lower abdominal and urogenital day surgery, and both blocks can be safely preferred for effective analgesia in the acute period.

ETHICS

Ethics Committee Approval: Our study was planned retrospectively on the basis of the Declaration of Helsinki principles, after University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Ethics Committee approval (decision no: 252 date: 27.07.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: N.A., D.A., F.G.Ö., Concept: N.A., D.A., F.G.Ö., Design: N.A., D.A., Data Collection or Processing: N.A., D.A., Analysis or Interpretation: N.A., Literature Search: N.A., D.A., F.G.Ö., Writing: N.A., D.A., F.G.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Oliver JA, Oliver LA, Aggarwal N, Baldev K, Wood M, Makusha L, et al. Ambulatory Pain Management in the Pediatric Patient Population. Curr Pain Headache Rep 2022;26:15-23.
2. Kumar A, Dogra N, Gupta A, Aggarwal S. Ultrasound-guided transversus abdominis plane block versus caudal block for postoperative analgesia in children undergoing inguinal hernia surgery: A comparative study. J Anaesthesiol Clin Pharmacol 2020;36:172-6.
3. Rahimzadeh P, Faiz SH. Ultrasound a new paradigm in regional anesthesia and pain management. Anesth Pain Med 2013;3:228-9.
4. Bonnet F, Berger J, Aveline C. Transversus abdominis plane block: what is its role in postoperative analgesia? Br J Anaesth 2009;103:468-70.
5. Abu Elyazed MM, Mostafa SF, Abdullah MA, Eid GM. The effect of ultrasound-guided transversus abdominis plane (TAP) block on postoperative analgesia and neuroendocrine stress response in pediatric patients undergoing elective open inguinal hernia repair. Paediatr Anaesth 2016;26:1165-71.
6. Hebbard PD. Transversalis fascia plane block, a novel ultrasound-guided abdominal wall nerve block. Can J Anaesth 2009;56:618-20.
7. Abdelbaser I, Mageed NA, El-Emam EM, ALseoudy MM, Elmorsy MM. Preemptive analgesic efficacy of ultrasound-guided transversalis fascia plane block in children undergoing inguinal herniorrhaphy: a randomized, double-blind, controlled study. Korean J Anesthesiol 2021;74:325-32.
8. Dontukurthy S, Mofidi R. The Role of Interfascial Plane Blocks in Paediatric Regional Anaesthesia: A Narrative Review of Current Perspectives and Updates. Anesthesiol Res Pract 2020;2020:8892537.
9. Kılınçoğlu N, Oba S, Paksoy I, Özbağrıaçık Ö. Comparison of postoperative analgesia methods in pediatric lower abdominal surgery.Med Bull Sisli Etfal Hosp 2006;40:19-24.
10. White PF. The changing role of non-opioid analgesic techniques in the management of postoperative pain. Anesth Analg 2005;101(5 Suppl):S5-22.
11. Fawy DME, Gendy HAE. Ultrasound-guided transverses abdominis plane block versus caudal block for postoperative pain relief in infants and children undergoing surgical pyeloplasty. Ains Shams J Anesth 2014;7:177-81.
12. Carney J, Finnerty O, Rauf J, Curley G, McDonnell JG, Laffey JG. Ipsilateral transversus abdominis plane block provides effective analgesia after appendectomy in children: a randomized controlled trial. Anesth Analg 2010;111:998-1003.
13. Kendigelen P, Tutuncu AC, Erbabacan E, Ekici B, Köksal G, Altındas F, et al. Ultrasound-assisted transversus abdominis plane block vs wound infiltration in pediatric patient with inguinal hernia: randomized controlled trial. J Clin Anesth 2016;30:9-14.
14. Ahiskalioglu A, Aydin ME, Doymus O, Yayik AM, Celik EC. Ultrasound guided transversalis fascia plane block for lower abdominal surgery: First pediatric report. J Clin Anesth 2019;55:130-1.
15. Peksöz U, Yayık AM, Çelik EC. Efficacy of ultrasound-guided transversalis fascia plane block in pediatric ureteroneocystostomy surgery. Korean J Anesthesiol 2022;75:188-90.
16. López-González JM, López-Álvarez S, Jiménez Gómez BM, Areán González I, Illodo Miramontes G, Padín Barreiro L. Ultrasound-guided transversalis fascia plane block versus anterior transversus abdominis plane block in outpatient inguinal hernia repair. Rev Esp Anestesiol Reanim 2016;63:498-504.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:319-323
DOI: 10.4274/BMJ.galenos.2023.2023.5-13

Research

Transforaminal Epidural Injections in Neurosurgical Clinical Practice: A Single Surgeon's Experience

Nöroşirürji Klinik Pratiğinde Transforaminal Epidural Enjeksiyon Uygulamaları; Tek Cerrah Deneyimi

Eylem Burcu Kahraman Özlü

University of Health Sciences Türkiye, İstanbul Haydarpaşa Training and Research Hospital, Clinic of Neurosurgery, İstanbul, Türkiye

ABSTRACT

Objective: The aim of this study was to retrospectively evaluate the success of transforaminal epidural injection (TFEI) in pain control among patients who presented with radicular pain based on a single surgeon's experience.

Methods: A total of 134 patients who presented to the Neurosurgery Clinic of Haydarpaşa Numune Training and Research Hospital, University of Health Sciences Türkiye between 2021 and 2022 and underwent TFEI procedures by the same surgeon were retrospectively evaluated. Patients were analyzed according to age, gender, Verbal Pain scale (VPS) values before and 5-7 days after the procedure, primary pathology, number of repetitions, history of spinal surgery before the procedure, and whether surgery was necessary after the procedure.

Results: The mean VPS evaluated before the procedure was 9.04 (10-6) among all patients. The mean VPS value was 3.48 (8-1) in the follow-up on the 5th-7th days after the procedure. Among the patients, 11 (8.2%) underwent surgery because pain control was not achieved. Two of these patients had spinal stenosis and nine had disk herniation.

Conclusion: TFEI is a successful method for ensuring pain management in suitable patients. It should be considered for lumbar radicular pain management in patients with different pathologies in the clinical practice of neurosurgery.

Keywords: Transforaminal epidural injection, pain, disk herniation, spinal

ÖZ

Amaç: Radiküler ağrı nedeniyle başvuran hastalara uygulanan transforaminal epidural enjeksiyonun (TFEE) ağrı kontrolündeki başarısının tek cerrah deneyimi üzerinden retrospektif olarak değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Sağlık Bilimleri Üniversitesi, Haydarpaşa Numune Eğitim Araştırma Hastanesi Beyin ve Sinir Cerrahisi Kliniği'ne 2021-2022 yıllarında başvuran, aynı cerrah tarafından TFEE işlemi uygulanan 134 olgu retrospektif olarak değerlendirildi. Olgular yaş, cinsiyet, işlem öncesi ve 5-7 gün sonrası Sözel Ağrı skalası (SAS) değerleri, primer patoloji, işlemin tekrarlanma sayısı, işlem öncesi omurga cerrahisi öyküsü ve işlem sonrası cerrahi ihtiyacı olup olmaması açısından tarandı.

Bulgular: Tüm olguların girişim öncesi değerlendirilen SAS ortalaması 9,04 (10-6) idi. İşlem sonrası 5-7. günlerde yapılan kontrolde SAS değeri ortalaması 3,48 (8-1) olarak değerlendirildi. Olguların 11 tanesine (%8,2) ağrı kontrolü sağlanamaması nedeniyle cerrahi girişim uygulandı. Bu olguların 2'si spinal stenozlu olgu, 9 tanesi disk hernisi olgusu idi.

Sonuç: TFEE uygun hastalarda ağrı kontrolünde başarılı bir yöntemdir. Nöroşirürji klinik pratiğinde lomber radiküler ağrı kontrolünde farklı patolojilerde hasta grubunda kullanımı akılda tutulmalıdır.

Anahtar Kelimeler: Transforaminal enjeksiyon, ağrı, disk hernisi, omurga

Address for Correspondence: Eylem Burcu Kahraman Özlü, University of Health Sciences Türkiye, İstanbul Haydarpaşa Training and Research Hospital, Clinic of Neurosurgery, İstanbul, Türkiye
Phone: +90 532 766 70 13 E-mail: burcu.kahraman@gmail.com ORCID ID: orcid.org/0000-0003-1662-1103

Cite as: Kahraman Özlü EB. Transforaminal Epidural Injections in Neurosurgical Clinical Practice: A Single Surgeon's Experience. Med J Bakirkoy 2023;19:319-323

Received: 31.05.2023
Accepted: 14.09.2023

INTRODUCTION

Pain is a complaint that significantly impairs the quality of life of individuals. It has been argued that healthy people experience 80-85% back pain throughout their lives. While 80-90% of acute back pain regresses in 6-8 weeks without treatment or regardless of the treatment method, 20-50% recur within a year, and 5% become chronic and persist for longer than six months (1). Intervertebral disk disorder is the most common cause of lumbago and sciatica, and surgical treatment is necessary in only 10-15% of patients (2). In most patients, complaints are eliminated using conservative methods. Conservative treatment methods include medical treatments, physical therapy, resting, weight loss, exercise, changing lifestyle, and epidural steroid injections (ESIs). ESI is a nonsurgical and minimally invasive treatment method commonly used for the treatment of lumbar disk herniations presenting with radicular symptoms. The first study on the epidural administration of steroids was published by Robecchi and Capra (3).

It has been argued that ESIs are effective in the treatment of local inflammatory changes and mechanical compression due to discopathy, which may cause root irritation (4). The cause of radicular pain was thought to be root compression; however, the inability to achieve pain control by removal of the pressure through surgery in some patients and the reduction of pain by ESIs suggested that there were causes of pain other than mechanical pressure on the nerve (5,6). An ESI can be performed interlaminar and/or transforaminal or from the sacral hiatus. In comparative studies on which approach is more effective, no significant superiority was found between the caudal, interlaminar, and transforaminal approaches (7). Today, the transforaminal approach has become more popular to ensure the transfer of a higher concentration of steroids to the target tissue. Studies have shown that selective transforaminal ESIs and local anesthetic injections are effective and safe treatment methods for managing radicular pain in lumbar radiculopathy (8).

Our study aimed to evaluate the effect of transforaminal ESI on pain management before and after surgery in patients with radicular pain, albeit secondary to various pathologies.

METHODS

In this study, 134 patients who presented to the Neurosurgery Clinic of Haydarpaşa Numune Training and Research Hospital, University of Health Sciences Türkiye between 2021 and 2022 and underwent TFEI procedures by the same surgeon were retrospectively evaluated after the approval of University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital at the TUEK meeting dated 29.11.2022 (no: E-62977267-771).

The study included patients who presented to the outpatient clinic with radicular pain secondary to various pathologies, had disk herniation and signs of spinal stenosis on magnetic resonance imaging, had no motor defects or progressive neurological loss, and had been administered ESI. Patients with extruded or sequestered disk herniation and motor deficit underwent the appropriate surgical procedure performed by the same surgeon. Patients were retrospectively examined in terms of age, gender, Verbal Pain scale (VPS) values before and 5-7 days after the procedure, primary pathology, number of repetitions of the procedure, history of spinal surgery before the procedure, and whether surgery was necessary after the procedure. The data in the study were evaluated by taking the arithmetic averages of the results obtained in the study.

The distance or distances to be intervened for the cases were decided by correlating the dermatomal spread of the pain mentioned at the time of admission to the outpatient clinic with the regions determined to have pressure during imaging.

All patients were orally informed about the procedure during admission to the outpatient clinic, their questions were answered, if any, and written consent was obtained before the procedure. Following the interventional procedures, all patients were invited for follow-up on the 5^{th}-7^{th} days to determine additional treatments, if necessary, and to evaluate the results of the procedure.

The patients were informed that they should have a light meal and take their regular medications on the day of the procedure. Unless there were any contraindications, medical treatments of patients using antiaggregant-anticoagulant were discontinued before the appropriate time according to the active substance. No sedation was administered to the patients during the procedure, and all procedures were performed under local anesthesia. The procedure was performed via the transforaminal route in all patients.

The TFEI procedure was performed in the operating room using C-arm fluoroscopy. The patient was placed in the prone position on the C-arm fluoroscopy table. The distance to perform the procedure was determined by obtaining images in the anteroposterior and lateral planes. Following this, the area was sterilized with a 10% povidone-iodine solution, and the patient was covered sterile.

After local infiltration anesthesia was administered with 5 mL of 2% subcutaneous lidocaine from the injection point at the specified distance, the intervertebral foramen was

reached with an 18 G 90 mm Quincke-type spinal needle accompanied by fluoroscopy. 1 mL of contrast agent was used for level verification. The contrasted area was observed to be the target area by fluoroscopy, and 20 mg (4 mL) and 40 mg methylprednisolone acetate were mixed with 0.5% bupivacaine for each level and injected to reach 5 mL in total. The mixture was prepared in the same amount and administered separately at each level. After the procedure, the patients were followed up in the clinic for 1 hour. Patients were recommended bed rest on the day of the procedure. They were advised to return to their daily routine the next day. Medications other than anticoagulant-antiaggregant treatments were continued, including the day of the procedure. They were recommended to restart anticoagulant and/or antiagregant treatments the next day. They were invited for follow-up on the 5th-7th day after the procedure.

The VPS values used in the study were obtained immediately before the procedure and during the evaluation of the outpatient clinic on the 5th-7th day of the patient.

RESULTS

The study was conducted with 134 patients (61 male, 73 female). The mean age of the patients was 53.96 (19-88). TFEI was performed from multiple distances in 25 patients. The procedure was performed from a single distance in other patients. In three patients, the procedure was performed for pain management following a failed back surgery (FBS). Spinal stenosis was in 10 patients. In other patients, a procedure was performed because of discogenic radicular pain. The procedure was repeated three times in 1 patient and twice in 9 patients with an interval of three months at the minimum. All patients who underwent repeated procedures had discogenic radicular pain. Facet joint block was also performed for accompanying back pain in all patients (n=13) who underwent surgery due to spinal stenosis and FBS.

The procedure was performed at the L2-3 distance in 1 patient, L3-4 distance in 43 patients, L4-5 distance in 98 patients, and L5-S1 distance in 14 patients. The procedure was performed at multiple distances in the same session, including two in 23 patients and three in 1 patient. The patient, who underwent the procedure at three distances in the same session, was diagnosed with spinal stenosis and could not undergo surgery because of accompanying diseases.

The VPS was used as the pain score in all patients. The most severe pain felt throughout life was scored as 10 and the mildest pain as 1. The mean VPS score of all patients was 9.04 (10-6) prior to the procedure. The mean VPS value was 3.48 (8-1) in the follow-up on the 5th-7th days following the procedure.

A surgical procedure was performed on 11 (8.2%) patients because of the inability to achieve pain control. Two of these patients had spinal stenosis and nine had disk herniation. In patients who did not benefit from the procedure and underwent surgery, the mean VPS value was 8.7 before the procedures. On the 5th-7th days following the procedure, it was observed to have regressed to 4.5. It was found that the pain recurred more than seven days later in patients who underwent surgery. The medical history of 15 patients who underwent TFEI included a surgical procedure in the lumbar region before the procedures. The surgery was performed at a different distance from where TFEI was administered, except for three patients with a history of FBS.

No significant major complications that caused labor loss were observed in any of the patients. A complaint of weakness in the lower extremity was detected in only 8 cases (5.9%) on the side of the unilateral procedure, which completely recovered between 6 and 8 hours. Six of the eight patients who developed paresis underwent the procedure at multiple distances. All patients were followed up in our clinic and discharged on the same day without any deficits. Vasovagal syncope developed in 2 patients (1.49%) and fully recovered upon intravenous fluid replacement. Temporary flushing, which improved spontaneously, was observed in 1 patient (0.74%). All these complications completely resolved without any sequelae. The frequency of minor complications was calculated to be 8.2% for all patients who underwent the procedure.

DISCUSSION

ESI has been used for many years as an effective method in the management of radicular pain in patients with radicular pain secondary to disk herniation, spinal stenosis, or spondylolisthesis and after FBS. ESIs can be performed through the caudal, interlaminar, and transforaminal routes. Caudal epidural injection was first published by Viner (9) in the 1920s. Procaine and saline injections were made through the caudal route during the procedure (9). In the 1960s, Brown (10) also published successful results with steroid injection into the epidural distance. In the clinical practice of neurosurgery, TFEIs are frequently used in patients with a wide spectrum of radicular pain.

It is believed that the mechanism of radicular pain causes root edema after increased vascular permeability due to inflammation secondary to pressure. Steroids applied in TFEI directly and/or indirectly suppress the synthesis and

accumulation of inflammatory agents such as arachidonic acid, phospholipases, and prostaglandins. Thus, acute inflammation is also limited (11). In many studies, it has been mentioned that the treatment of radicular pain with TFEI in the early period provides more effective pain control compared with the chronic process (12). In our clinical practice, we perform TFEI injections on the same day or within one week following the admission of the patients in the acute painful period, if possible. Following the procedure, we observed that the quality of life of the patient improved, and the patient returned to daily life more quickly. This facilitates the rapid return of the person to their roles in life, except for the loss of the workforce.

Many studies have mentioned the necessity of using contrast agents and fluoroscopy in ESIs (13). In our clinical practice, we provide effective access to the target tissue using C-arm fluoroscopy and contrast agents in all TFEI injection procedures.

In our study, we used the VPS as the pain score in all patients in the retrospective evaluation of patients who underwent TFEI. In our clinical practice, we check the VPS values during patient follow-up. The most severe pain felt in the life of the patients was scored as 10 points, and the mildest pain as 1 point. The mean VPS score of all patients was 9.04 (10-6) before the procedure. In the follow-ups performed on the 5th-7th days after the procedure, the mean VPS value was found to be 3.48 (8-1). There was a prominent decrease in pain levels compared with those before the procedure. There was a significant decrease in the VPS values of all patients. Unlike other studies, significant regression was observed in the VPS values of patients with spinal stenosis. This difference was thought to be associated with the small number of patients with spinal stenosis in our sample. The highest benefit was determined in the patient group with disk herniation, which is consistent with the literature. Unlike our study, Taşdemir and Aydın (14) found that pain management was less successful in patients with spinal stenosis than in patients with FBS and disk herniation. Other studies have determined higher success rates in patients with disk herniation and limited success rates in patients with FBS and spinal stenosis (15,16).

In our study, 11 patients required surgical intervention because of the recurrence or exacerbation of pain in their follow-ups after the TFEI procedure. Nine of these patients had disk herniation and two had spinal stenosis. Four patients with disk hernia that required surgery were patients with surgical indications for whom pain control was intended during the preparation period until surgery. All patients underwent surgery by the same surgeon who performed the TFEI procedure.

In the literature, minor complications (transient root total block, contrast-associated side effects, vasovagal syncope, flushing, etc.) have been frequently reported concerning TFEI injections. Major complications such as exitus, discitis, or cardiac arrest have been reported in sporadic patients. In their study on 375 patients, Taşdemir and Aydın (14) reported pain at the injection site in 7 patients, increased complaints before the procedure in 4 patients, weight gain in 2 patients, and no major complications in any patient. Botwin et al. (17) reported the percentage of minor complications as 9.6%. Çetin et al. (18) reported that no major complications were encountered, and the percentage of minor complications was 11.1%. In our study, no significant major complications causing loss of labor force were observed in any of the patients, and the frequency of minor complications was calculated as 8.2% for all patients treated, in compliance with the literature.

We believe that TFEI is an efficient, easy, and inexpensive method for the management of radicular pain, which constitutes a significant part of neurosurgical clinical practice. We observed that effective treatment with appropriate indications increased the quality of life of the patient, facilitating the return to work and improving comfort in daily life activities. From our point of view, the fact that this study was a single surgeon experience is noteworthy in terms of closely monitoring the success of the procedure, complications, and progress in cases in need of surgery; however, we believe that it can be supported with a further retrospective study with long-term follow-up and a control group.

CONCLUSION

We believe that TFEI, which is used in the practice of spinal surgery for the management of radicular pain in patients with acute pain, patients who cannot undergo surgery due to comorbid pathologies, and patients with pain and preparing for surgery, is an efficient treatment method that should be considered by neurosurgeons.

ETHICS

Ethics Committee Approval: Approval of University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital was received at the TUEK meeting dated 29.11.2022 (no: E-62977267-771).

Informed Consent: All patients were orally informed about the procedure during admission to the outpatient clinic, their questions were answered, if any, and written consent was obtained before the procedure.

Financial Disclosure: The author declare that this study received no financial support.

REFERENCES

1. Reilly PA. Occupational low back pain. J Rheumatol 2001;28:225-6.
2. Deyo RA, Mirza SK, Martin BI. Back pain prevalence and visit rates: estimates from U.S. national surveys, 2002. Spine (Phila Pa 1976) 2006;31:2724-7.
3. ROBECCHI A, CAPRA R. L'idrocortisone (composto F); prime esperienze cliniche in campo reumatologico [Hydrocortisone (compound F); first clinical experiments in the field of rheumatology]. Minerva Med 1952;43:1259-63.
4. Manchikanti L, Datta S, Gupta S, Munglani R, Bryce DA, Ward SP, et al. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: part 2. Therapeutic interventions. Pain Physician 2010;13:E215-64.
5. McLain RF, Kapural L, Mekhail NA. Epidural steroid therapy for back and leg pain: mechanisms of action and efficacy. Spine J 2005;5:191-201.
6. Manchikanti L, Cash KA, Pampati V, Falco FJ. Transforaminal epidural injections in chronic lumbar disc herniation: a randomized, double-blind, active-control trial. Pain Physician 2014;17:E489-501.
7. Manchikanti L, Singh V, Pampati V, Falco FJ, Hirsch JA. Comparison of the efficacy of caudal, interlaminar, and transforaminal epidural injections in managing lumbar disc herniation: is one method superior to the other? Korean J Pain 2015;28:11-21.
8. Cohen SP, Bicket MC, Jamison D, Wilkinson I, Rathmell JP. Epidural steroids: a comprehensive, evidence-based review. Reg Anesth Pain Med 2013;38:175-200.
9. Viner N. Intractable Sciatica. The Sacral Epidural Injection; An Effective Method of Giving Relief. Can Med Assoc J 1925;15:630-4.
10. BROWN JH. Pressure caudal anesthesia and back manipulation. Conservative method for treatment of sciatica. Northwest Med 1960;59:905-9.
11. Guldogus F. Epidural steroid injection. Inside: Erdine S, editor. Pain. 3rd edition. Istanbul: Nobel Medical Bookstores; 2007. p. 686-9.
12. Derincek A, Eker E, Pourbagher A, Cınar MB, Ozalay M. Epidural steroid enjeksiyonu: Başarı tahmin edilebilir mi? [Lumbar epidural steroid injection: Is the success rate predictable?]. Agri 2011;23:147-52.
13. Abdi S, Datta S, Trescot AM, Schultz DM, Adlaka R, Atluri SL, et al. Epidural steroids in the management of chronic spinal pain: a systematic review. Pain Physician 2007;10:185-212.
14. Taşdemir BB, Aydın ON. Bel ağrılı hastalarda transforaminal anterior epidural steroid enjeksiyonunun etkinliğinin ve girişimsel tedavinin yaşam kalitesine etkisinin retrospektif araştırılması. Agri 2019;31:93-100.
15. Botwin KP, Gruber RD, Bouchlas CG, Torres-Ramos FM, Sanelli JT, Freeman ED, et al. Fluoroscopically guided lumbar transformational epidural steroid injections in degenerative lumbar stenosis: an outcome study. Am J Phys Med Rehabil 2002;81:898-905.
16. Lee JW, Kim SH, Lee IS, Choi JA, Choi JY, Hong SH, et al. Therapeutic effect and outcome predictors of sciatica treated using transforaminal epidural steroid injection. AJR Am J Roentgenol 2006;187:1427-31.
17. Botwin KP, Gruber RD, Bouchlas CG, Torres-Ramos FM, Freeman TL, Slaten WK. Complications of fluoroscopically guided transforaminal lumbar epidural injections. Arch Phys Med Rehabil 2000;81:1045-50.
18. Çetin MF, Karaman H, Ölmez Kavak G, Tüfek A, Baysal Yildirim Z. Lumbar radikülopatili hastalarda transforaminal lumbar epidural steroid enjeksiyonlarının etkinliği [Efficacy of transforaminal lumbar epidural steroid injections in patients with lumbar radiculopathy]. Agri 2012;24:77-84.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:324-327
DOI: 10.4274/BMJ.galenos.2023.2023.5-9

Research

Adolescent Idiopathic Scoliosis Surgery Decision Making with Fuzzy Model

Adölesan İdiyopatik Skolyoz Cerrahisi Kararında Bulanık Model Kullanımı

Gürkan Berikol[1], Uzay Erdoğan[2]

[1]University of Health Sciences Türkiye, İstanbul Taksim Training and Research Hospital, Clinic of Neurosurgery, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, İstanbul Bakırköy Prof. Dr. Mazhar Osman Mental Health and Nervous Diseases Training and Research Hospital, Clinic of Neurosurgery, İstanbul, Türkiye

ABSTRACT

Objective: The surgical decision in scoliosis patients exhibits variability based on angle parameters and the characteristics of patients in the adult or adolescent age group. Existing studies demonstrate that the Cobb's angle, particularly in the range of 25-45, shapes the surgical decision depending on the measures and characteristics of the patients. This study evaluated the performance of a fuzzy logic-based decision support system in making surgical decisions.

Methods: A total of 888 patient scenarios were generated in a computer environment, with age, Cobb's, and Risser values. Surgical probability predictions were recorded according to the values in the patient scenarios using rules established by field experts through fuzzy modeling.

Results: Although surgical necessity was found in 28.8% of the patients in the reference model, the model detected it at a rate of 11.6%. The sensitivity of the model was 33.9% [95% confidence interval (CI) 27.8-39.7%], specificity 97.3% (95% CI 95.7-98.4%), positive predictive value 83.5% (95% CI 74.9-90.1%), negative predictive value 78.34% (95% CI 75.3-81.2%), accuracy 78.9% (76.1-81.6%), Youden index 0.308, and area under the curve value 0.654.

Conclusion: Fuzzy logic is a viable method, particularly in situations where boundaries cannot be clearly determined. Considering variables such as Cobb's and Risser in scoliosis surgery, it could be a method to use in the choice of surgery or conservative follow-up.

Keywords: Fuzzy logic, scoliosis, spinal surgery, Risser, Cobb's

ÖZ

Amaç: Skolyoz hastalarında cerrahi kararı açı parametreleri ve hastaların yetişkin ya da adölesan yaş grubu özelliklerine göre değişkenlik göstermektedir. Yapılan çalışmalarda Cobb açısı özellikle 25-45 aralığında cerrahi kararı kişisel özelliklere, ölçümlere ve hasta özelliklerine bağlı olmaktadır. Çalışmamızda bulanık mantık tabanlı karar destek sisteminin cerrahi kararı vermedeki performansını ölçmek amaçlanmıştır.

Gereç ve Yöntem: Bilgisayar ortamında oluşturulan 888 hasta senaryosu yaş, Cobb ve Risser değerleri oluşturulmuştur. Bulanık modellemesi ile alan uzmanlarınca oluşturulan kurallar ile hasta senaryolarındaki değerlere göre cerrahi olasılık tahminleri kaydedilmiştir.

Bulgular: Referans modelde cerrahi gereklilik %28,8 hastada bulunurken model %11,6 oranında saptandı. Modelin duyarlılığı %33,9 [%95 güven aralığı (GA) %27,8-39,7], özgüllüğü %97,3 (%95 GA %95,7-98,4), pozitif prediktif değeri %83,5 (%95 GA %74,9-90,1), negatif prediktif değeri %78,34 (%95 GA %75,3-81,2), doğruluk %78,9 (%76,1-81,6), Youden indeks 0,308 ve eğrinin altındaki alan değeri 0,654 olarak bulunmuştur.

Sonuç: Bulanık mantık özellikle sınırları net belirlenemeyen durumlarda kullanılabilir bir yöntemdir. Skolyoz cerrahisinde Cobb, Risser gibi değişkenler de ele alındığında, cerrahi ya da konservatif takip seçiminde kullanılabilecek bir yöntem olabilir.

Anahtar Kelimeler: Bulanık mantık, skolyoz, spinal cerrahi, Risser, Cobb's

Address for Correspondence: Gürkan Berikol, University of Health Sciences Türkiye, İstanbul Taksim Training and Research Hospital, Clinic of Neurosurgery, İstanbul, Türkiye
Phone: +90 553 393 28 25 E-mail: dr.berikol@gmail.com ORCID ID: orcid.org/0000-0001-6434-8143

Cite as: Berikol G, Erdoğan U. Adolescent Idiopathic Scoliosis Surgery Decision Making with Fuzzy Model. Med J Bakirkoy 2023;19:324-327

Received: 31.05.2023
Accepted: 14.09.2023

INTRODUCTION

Adolescent idiopathic scoliosis (AIS), one of the most common types of scoliosis, presents symptoms before adulthood and emerges when the spine angulation of 10° or more. Idiopathic scoliosis, particularly in those over 10 years of age, is a disease that requires treatment because of its progressive nature and its impact on other systems such as the cardiovascular system (1,2).

Physiological factors, such as age, body mass index, bone density, and radiological scales, such as the Risser score, Cobb's angle, and Sanders, determine the progression of the disease and the need for surgery (2). The most determinant variables for diagnosis are the size of the curve and skeletal density. As these are also the most determinant variables of progression, they are used in making the decision for surgery.

Particularly in AIS treatment, having a Cobb's angle of 45° and above, the patient's age leading to an increase in the growth rate of scoliosis, functional limitation, and response to physiotherapy or bracing affects the surgical decision (3). In patients without skeletal maturity, a Cobb's angle of ≥50° is a clear surgical indication, whereas in some immature patients above 45° or in some mature patients ≥50°, surgical indication can still be made (4). The correct surgical decision should be made on a patient-by-patient basis. Performing surgery when necessary can prevent the patient's progression to respiratory and cardiovascular insufficiency, while also protecting the patient against complications such as blood loss, implant insufficiency, and infections. In a systematic review, it was stated that there are still limitations for clinical use in the studies conducted, and there is a need for artificial intelligence studies for spinal curvature prediction (2).

Fuzzy logic is an artificial intelligence model that is based on the "if...then" logic and is carried out with the weighting of the evaluation's membership to clusters with the help of a set of linguistic rules (5). In this context, a variable can be included in more than one class with different weights (6). This method helps in the classification of random variables that are difficult to belong to a certain class. This method, which is used in areas such as engineering and biology, has been studied in many areas of medicine in recent years (7-9).

The study evaluated the performance of the fuzzy logic model in determining the surgical decision for AIS.

METHODS

In our study, the fuzzy logic model was used to make surgical decisions with the variables used in the guidelines. The study methodology involved creating surgical or bracing outputs in an *in silico* model using inputs such as age, Cobb's angle, and Risser score using FuzzyTech 8.21c Professional Edition on Windows 10 (Licence no: Akdeniz University 1000700). The rules and membership functions are shown in Figure 1 and Table 1. The Center of Maximum defuzzification model was chosen because of the clarity of the decision for surgical or conservative treatment. The fuzzy rules related to surgical decisions were made in line with the prediction scores found in the literature and were confirmed by field experts (10-13).

To validate the system model and measure its performance, 888 patient scenarios were created, with Cobb's angles and Risser scores ranging from 23° to 46° according to age between 9 and 16 years and treatment predictions were recorded in the model.

Eighty-one rules (25 partial rules) were generated. The generated example rules are shown in Table 2.

The results of the model were compared with those of the Risser score calculation tools used in literature-based practice, and their performances were tested with sensitivity, specificity, accuracy, and F1 score using the Jamovi 1.6.21 program.

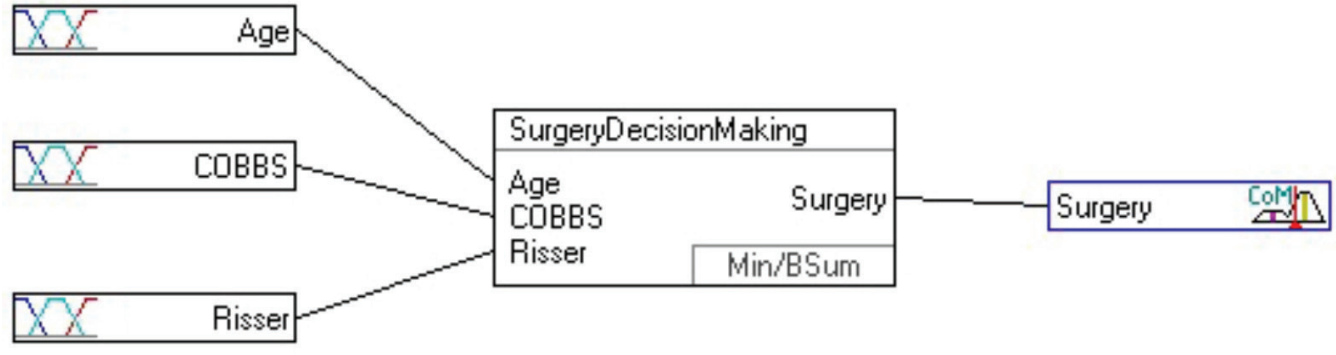

Figure 1. Structure of the fuzzy logic system

Table 1. Variables of input and output

#	Variable name	Type	Unit	Min	Max	Default	Term names
1	Age		Age	0	20	15	Childhood Adolescent Adult
2	Cobb's		Degree	0	100	0	Low Medium High
3	Risser		Scale	0	2	2	Low Medium High
4	Surgery		SurgeryNeed	-1	1	0	Low Medium High

Min: Minimum, Max: Maximum

Table 2. Examples of rules and membership weights. For example, IF age is "high" Cobb's "high", Risser "high", then surgery is "high likely"

Age	Cobb's	Risser	DoS	Surgery
9	11	0	1.0	Low likely
9	12	0	1.0	Low likely
16	42	1	1.0	Intermediate
16	43	1	1.0	Intermediate
16	46	1	1.0	High likely
16	47	1	1.0	High likely

Table 3. Crosstable of the surgery likelihood of reference and model

		Reference score calculators		
		Low	Intermediate	High
Fuzzy model	Low	74	10	0
	Intermediate	370	161	170
	High	2	15	86

RESULTS

In our study, among the 888 patient scenarios, 28.8% (256/888) were potential surgical candidates, whereas the model identified a surgical likelihood of 11.6% (103/888). The cross-table according to the model and reference is shown in Table 3.

The sensitivity of the model was determined as 33.9% [95% confidence interval (CI) 27.8-39.7%], specificity as 97.3% (95% CI 95.7-98.4%), positive predictive value as 83.5% (95% CI 74.9-90.1%), and negative predictive value as 78.34% (95% CI 75.3-81.2%).

The accuracy was found to be 78.9% (76.1%-81.6%), the Youden index was 0.308, and the area under the curve value was 0.654 (Figure 2).

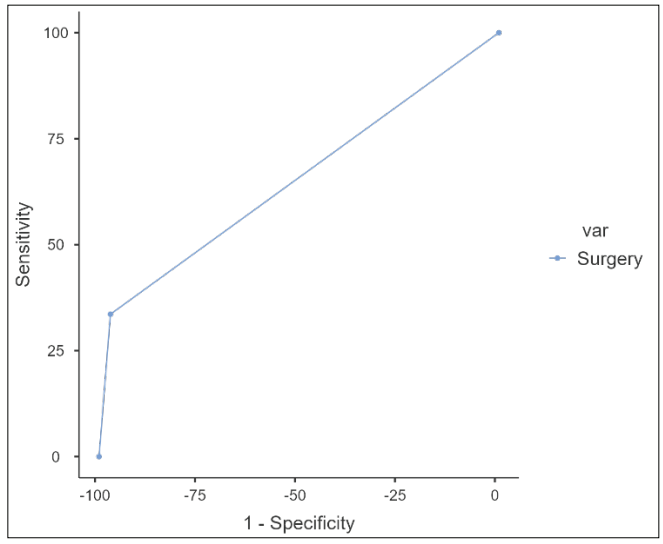

Figure 2. ROC curve of the fuzzy model
ROC: Receiver operating characteristic

DISCUSSION

In our study, traditional calculation models and fuzzy models were compared in a scenario of 888 patients, and it was determined that they could be used in surgical decisions with a specificity of 97.3%. In the review conducted, the top five factors determining the prognosis of scoliosis were curvature speed, skeletal maturity, location of the curvature, age, and menarche status. In our study, age, skeletal maturity with Risser, and Cobb's angle were taken into account (2). Gender was taken as female in reference calculators because it was not stated as a determinant (10,11,13).

In the literature, there are artificial intelligence-based decision support systems for the diagnosis and management of scoliosis. In the fuzzy logic model calculating Cobb's angle in spinal graphs using the Schroth method by Goral

and Kose (14), the accuracy of suggestions for diagnosis and exercises for physiotherapy is 0.98. Again, it has been reported that the prediction of Cobb's angle with image processing and machine learning in the decision of spinal fusion surgery, especially whether it is less than <10°, can predict with an accuracy of 86.23% (15).

As indicated in the literature, ≥50° is suggested to have surgery with a high evidence level regardless of maturity and time, and ≥45° and Risser <2 is suggested to have surgery with a lower evidence level (4). The decision to postpone the surgical option as much as possible varies according to the follow-up of spinal surgeons and patients. Therefore, machine learning has been used in the literature especially for predicting the necessity of surgical intervention, and a decision support system based on random forest has been developed, which optimizes surgical decisions according to the final Cobb's angle estimate using the most predictive variables, Cobb's angle, flexibility, age, and Risser criteria (16). In addition, the progression of curvature was developed with a logistic regression model, and in the prediction made with Cobb's, Menarche, weight, Risser, plasma microRNA, and bone turnover markers, a specificity of 90% and a sensitivity of 72.7% were determined (17).

In addition, a decision support system was developed by working on deciding on surgical treatment using a fuzzy logic-based clustering algorithm on a diagnostic classification with early onset scoliosis classification using age, etiology, Cobb's angle, and kyphosis variables (18).

Our study is preliminary, and the non-use of real patient data limits our study. Further studies require this system to be validated with real-life data. In addition, our model includes other variables, such as growth rate and Sanders. The model results can be improved by adding these criteria.

CONCLUSION

In our study, the use of fuzzy logic modeling in making surgical decisions in AIS with Cobb's, Risser, and age variables emerged as a method that could be used in the selection of surgical patients with high specificity. We believe that by increasing the variables in future studies and validating with real outcomes, the model can achieve a higher accuracy rate.

ETHICS

Ethics Committee Approval: The study does not require ethics committee approval.

Informed Consent: The study does not require patient consent.

Authorship Contributions

Concept: G.B., U.E., Design: G.B., U.E., Data Collection or Processing: G.B., U.E., Analysis or Interpretation: G.B., U.E., Literature Search: G.B., U.E., Writing: G.B., U.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Scherl SA, Hasley BP. Adolescent idiopathic scoliosis: Clinical features, evaluation, and diagnosis UpToDate; 2023.
2. Lenz M, Oikonomidis S, Harland A, Fürnstahl P, Farshad M, Bredow J, et al. Scoliosis and Prognosis-a systematic review regarding patient-specific and radiological predictive factors for curve progression. Eur Spine J 2021;30:1813-22.
3. Negrini S, Donzelli S, Aulisa AG, Czaprowski D, Schreiber S, de Mauroy JC, et al. 2016 SOSORT guidelines: orthopaedic and rehabilitation treatment of idiopathic scoliosis during growth. Scoliosis Spinal Disord 2018;13:3.
4. Scherl SA, Hasley BP. Adolescent idiopathic scoliosis: Management and prognosis. In UpToDate, Waltham, MA; 2023. https://www.uptodate.com/contents/adolescent-idiopathic-scoliosis-management-and-prognosis
5. Klir GJ, Yuan B. Fuzzy sets and fuzzy logic: theory and applications. Upper Saddle River, N.J: Prentice Hall PTR; 1995. p. 574. http://www.pzs.dstu.dp.ua/logic/bibl/yuan.pdf
6. Zadeh LA. Fuzzy sets. Information and Control 1965;8:338–53.
7. Mahfouf M, Abbod MF, Linkens DA. A survey of fuzzy logic monitoring and control utilisation in medicine. Artif Intell Med 2001;21:27-42.
8. Phuong NH, Kreinovich V. Fuzzy logic and its applications in medicine. Int J Med Inform 2001;62:165-73.
9. Abbod MF, Von Keyserlingk DG, Linkens DA, Mahfouf M. Survey of utilisation of fuzzy technology in Medicine and Healthcare. Fuzzy Sets and Systems 2001;120:331–49.
10. Idiopathic Scoliosis Progression Risk Calculator. https://scoliosiscarecenters.com/idiopathic-scoliosis-progression-risk-calculator/
11. Risser Model for Predicting the Prognosis of Adolescent Idiopathic Scoliosis (AIS) at Skeletal Maturity. https://uihc.org/childrens/risser-model-predicting-prognosis-adolescent-idiopathic-scoliosis-ais-skeletal-maturity
12. Lonstein JE, Carlson JM. The prediction of curve progression in untreated idiopathic scoliosis during growth. J Bone Joint Surg Am 1984;66:1061-71.
13. BrAIST-Calc. https://hydroinformatics.uiowa.edu/lab/braist_calc/calc.html
14. Goral S, Kose U. Development of a CapsNet and Fuzzy Logic Decision Support System for Diagnosing the Scoliosis and Planning Treatments via Schroth Method. IEEE Access 2022;10:129055–78.
15. Vyas D, Ganesan A, Meel P. Computation and Prediction Of Cobb's Angle Using Machine Learning Models. In: 2022 2nd International Conference on Intelligent Technologies (CONIT) [Internet]. Hubli, India: IEEE; 2022. p. 1–6. https://ieeexplore.ieee.org/document/9847938/
16. Alfraihat A, Samdani AF, Balasubramanian S. Predicting curve progression for adolescent idiopathic scoliosis using random forest model. PLoS One 2022;17:e0273002.
17. Zhang J, Cheuk KY, Xu L, Wang Y, Feng Z, Sit T, et al. A validated composite model to predict risk of curve progression in adolescent idiopathic scoliosis. EClinicalMedicine 2020;18:100236.
18. Viraraghavan G, Cahill PJ, Vitale MG, Williams BA; Pediatric Spine Study Group; Balasubramanian S. Automated Clustering Technique (ACT) for Early Onset Scoliosis: A preliminary report. Spine Deform 2023;11:723-31.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:328-338
DOI: 10.4274/BMJ.galenos.2023.2023.5-14

Research

Results of Microsurgical Clipping of Anterior Circulation Aneurysms Secondary to Subarachnoid Hemorrhage: 107 Cases

Subaraknoid Kanama ile Prezente Anterior Sistem Anevrizmalarının Mikrocerrahi Klipleme Cerrahi Sonuçları: 107 Olgu

Buruç Erkan, Ebubekir Akpınar, Yusuf Kılıç, Suat Demir, Ozan Barut, Ozan Haşimoğlu, Fahir Şencan, Lütfi Şinasi Postalcı

University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Neurosurgery, İstanbul, Türkiye

ABSTRACT

Objective: Spontaneous subarachnoid hemorrhage (sSAH) is a significant disease requiring urgent intervention. It may develop because of the rupturing of intracranial aneurysms and has high mortality and morbidity rates. This study was conducted at a hospital that serves as a reference center in the region in which it is located with the aim of evaluating patient characteristics, patient preferences, and complication management among patients with aneurysmal subarachnoid hemorrhage (aSAH) and presenting the results of these intracranial aneurysm clipping surgeries.

Methods: Cases of 261 patients who were admitted with a diagnosis of sSAH were retrospectively examined. Subsequently, 107 patients with aSAH who were treated with 117 microsurgical aneurysm clippings were included in the study. The effects of patient demographics, Glasgow coma scale (GCS) scores, clinical World Federation of Neurological Surgeons scale and Hunt/Hess scale scores, and radiological modified Fisher scale gradings on modified Rankin scale (mRS) scores were examined. The management of complications such as rebleeding, cerebral vasospasm (CV), and delayed cerebral ischemia and surgical results were compared according to clinical and radiological data.

Results: Of the patients, 52 were female (48%) and 55 were male (52%). Their average age was 50.4 years (range: 29-78 years), and the mean follow-up period was 13.8 months or 414 days (range: 30-892 days). The most common complaint of the patients at admission was headache (75.8%). Approximately 72.9% of patients had GCS scores of 14 or 15 at first admission. Twenty-eight (26.1%) patients had multiple aneurysms. Thirteen (12%) patients required a permanent cerebrospinal fluid drainage system. Rebleeding occurred in 7 (6.5%) patients before treatment. Thirty-six (33.6%) patients had a clinical CV. Delayed cerebral ischemia occurred in 25 (23.3%) patients. At the end of the mean follow-up period of 13.8 months, 82.3% of the patients had slight or no disabilities (mRS: 0-2), whereas 11.2% had severe disabilities (mRS: 3-5). Seven (6.5%) patients died, thus having an mRS score of 6 (exitus). Five (4.6%) patients had residual aneurysms. Six (5.6%) patients had parent or perforating artery occlusion.

Conclusion: Poor prognosis at admission, rebleeding, and CV complications remain the most important causes of mortality and morbidity related to aSAH. Evaluations of the diagnoses, treatments, and complication management of patients with sSAH and the multidisciplinary approaches of experienced endovascular and neurosurgical teams are important for better understanding and management of this disease.

Keywords: Cerebral vasospasm, rebleeding, modified Fisher scale, mortality, morbidity

ÖZ

Amaç: Spontan subaraknoid kanama (sSAK) acil müdahale gerektiren önemli bir hastalıktır. İntrakraniyal anevrizmaların yırtılmasına bağlı olarak gelişebilir ve yüksek mortalite ve morbidite oranlarına sahiptir. Bu çalışma, bulunduğu bölgenin referans bir merkez hastanesinde olup, başvuran anevrizmal subaraknoid kanama (aSAK) hastalarının özelliklerini, hastaların seçim ve komplikasyon yönetimini tartışmayı ve intrakraniyal anevrizma kliplenmesi cerrahisi sonuçlarını literatüre sunmayı amaçlamaktadır.

Gereç ve Yöntem: sSAK ile gelen 261 hasta retrospektif olarak incelendi. Yüz on yedi mikrocerrahi anevrizma klipleme operasyonu ile tedavi edilen 107 aSAK hastası çalışmaya dahil edildi. Hastaların demografik verileri, Glasgow koma skalası (GKS) skorları, klinik World Federation of

Address for Correspondence: Buruç Erkan, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Neurosurgery, İstanbul, Türkiye
Phone: +90 507 992 33 34 E-mail: burucerkan@hotmail.com ORCID ID: orcid.org/0000-0001-8586-0613

Cite as: Erkan B, Akpınar E, Kılıç Y, Demir S, Barut O, Haşimoğlu O, Şencan F, Postalcı LŞ. Results of Microsurgical Clipping of Anterior Circulation Aneurysms Secondary to Subarachnoid Hemorrhage: 107 Cases. Med J Bakirkoy 2023;19:328-338

Received: 03.06.2023
Accepted: 14.09.2023

Neurological Surgeons ve Hunt/Hess skalası skorları ve radyolojik modifiye Fisher sınıflamalarının modifiye rankin skalası (mRS) skorları üzerine olan etkileri incelendi. Tekrar kanama, serebral vazospazm, gecikmiş serebral iskemi gibi komplikasyonların yönetimi literatür ışığında tartışılmış ve cerrahi sonuçlar klinik ve radyolojik verilerle karşılaştırılmıştır.

Bulgular: Hastaların 52'si kadın (%48), 55'i erkekti (%52). Ortalama yaşları 50,4 (dağılım: 29-78 yıl), ortalama takip süresi 13,8 ay veya 414 gündü (dağılım: 30-892 gün). Hastaların başvuru anında en sık şikayeti baş ağrısıydı (%75,8). Hastaların %72,9'unun ilk başvuruda GKS skorları 14 veya 15'ti. Yirmi sekiz (%26,1) hastada çoklu anevrizma saptandı. On üç (%12) hastada kalıcı beyin omurilik sıvısı drenaj sistemi gerekti. Tedavi öncesinde 7 (%6,5) hastada tekrar kanama meydana geldi. Otuz altı (%33,6) hastada serebral vazospazm kliniği vardı. Gecikmiş serebral iskemi 25 (%23,3) hastada görüldü. Ortalama 13,8 aylık takip süresi sonunda hastaların %82,3'ü hafif engelli veya engelsiz (mRS: 0-2), %11,2'si ağır engelli (mRS: 3-5) seyretti. mRS skoru 6 (eksitus) olan 7 (%6,5) hasta mevcuttu. Beş (%4,6) hastada rezidü anevrizma tespit edildi. Altı (%5,6) hastada parent veya perforan arter oklüzyonu görüldü.

Sonuç: Başvuru anında kötü prognoz olması, tekrar kanama, serebral vazospazm gibi komplikasyonlar, aSAK'ye bağlı mortalite ve morbiditenin en önemli nedenleri arasında olmaya devam etmektedir. sSAK'lı hastaların tanı, tedavi ve komplikasyon yönetiminin deneyimli endovasküler ve nöroşirürji ekiplerinin multidisipliner yaklaşımları ile değerlendirilmesi bu hastalığın daha iyi anlaşılması ve yönetilmesi için önemlidir.

Anahtar Kelimeler: Serebral vazospazm, rebleeding, modifiye Fisher skalası, mortalite, morbidite

INTRODUCTION

Spontaneous subarachnoid hemorrhage (sSAH) is a clinical entity that causes high rates of mortality and morbidity, although it is responsible for only 1-7% of all strokes (1). In the past few decades, new diagnostic techniques, advances in neuroanesthesia, and technical developments in surgical clipping and endovascular methods have revolutionized the treatment of aneurysmal subarachnoid hemorrhage (aSAH), decreasing the annual mortality rates by 0.5-0.8% (2,3). Although mortality rates have decreased in developed countries over the last 25 years, this group of patients still experiences mortality rates of 32% to 67%, while one-third of survivors become permanently disabled (2-7).

Despite alternative methods devised by interventional radiologists for the treatment of aSAH secondary to intracranial aneurysms, such as coiling and stenting, microsurgical clipping remains a precise and permanent treatment method. The aim of this treatment is to completely close the aneurysm dome and protect the parent and perforating arteries (8-10).

On the other hand, treatment modalities for managing complications related to aSAH have still not been elucidated (11). The most common complication of aSAH is rebleeding. For untreated aneurysms, the risk of rebleeding is 20-30% in the first month and 3% per year in the following years. aSAH significantly increases mortality and morbidity. It is associated with mortality at a rate of approximately 67% (12,13). Cerebral vasospasm (CV) and delayed cerebral ischemia secondary to CV, which are observed in the middle and late stages of aSAH, are among the foremost complications. CV is responsible for 50% of the morbidity and mortality of patients who survive the first hemorrhage (14). The pathophysiology, prophylaxis, and treatment of CV are still major topics of discussion (11).

This study was conducted at a hospital that serves as a reference center in the region in which it is located with the aim of evaluating patient characteristics, patient preferences, and complication management of patients with aSAH and presenting the results of these intracranial aneurysm clipping surgeries.

METHODS

Patient Group

This study was conducted in a single center and included the results of operations performed by a single surgical team. A total of 107 patients operated on due to aSAH between September 2020 and November 2022 were included in the study. After obtaining approval for the study from the Ethics Committee of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital (decision no: 358, date: 16.08.2023), all data were retrospectively compiled and reviewed. All patients underwent non-contrast brain computed tomography (CT) scanning and digital subtraction angiography (DSA) before treatment for diagnostic purposes. Patients with internal carotid artery aneurysms were also scanned with contrast brain CT angiography to evaluate the relationship of the aneurysms with bones. All patients consulted interventional radiologists and were scheduled to undergo microsurgical clipping or endovascular treatment according to factors such as the morphology of the aneurysm and its placement, the preferences of patients and/or their representatives, and the center's caseload.

During the study period, 261 patients diagnosed with sSAH were treated in our clinic. No vascular pathology was detected in the first DSA examinations of 53 patients (20.3%), whereas 39 patients (15%) had pathologies not associated with intracranial aneurysms (e.g., arteriovenous malformation, arteriovenous fistula, and sinus vein

thrombosis). Intracranial aneurysm was the cause of sSAH in 169 (64.7%) patients. While 62 (23.7%) patients were treated for aSAH with endovascular methods by interventional radiologists, 107 (41%) patients underwent microsurgical aneurysm clipping as the first treatment for aSAH.

Patients treated for unruptured intracranial aneurysms, patients who were admitted because of sSAH but had no vascular pathologies or had intracranial aneurysms and/or non-aneurysm pathologies, and patients whose primary treatment and long-term follow-up were overseen by interventional radiologists as per the decision of the council were excluded from the study.

Patient demographics, comorbidities, clinical World Federation of Neurological Surgeons (WFNS) scale scores (15), Hunt/Hess scale (H/HS) scores (16), and radiological modified Fisher scale (mFS) scores (17) were analyzed considering modified Rankin scale (mRS) scores (18) and patient records.

Surgical Procedure

Traditional pterional craniotomy was used as the surgical technique for anterior circulation aneurysms, whereas median craniotomy, which allows an interhemispheric approach, was used as the surgical technique for distal anterior cerebral artery aneurysms. In accordance with microsurgical principles, the chiasmatic cisterns, carotid cisterns, and, if necessary, lamina terminalis cisterns of the patients were opened, sylvian fissures were dissected, proximal arteries were explored starting from around the aneurysm and perforating arteries, and, especially in cases of large aneurysms, venous structures adhered to the aneurysm dome were dissected from the neck of the aneurysm. The proximal parent arteries of most patients, not including patients with small aneurysms, were temporarily clipped. Temporary clipping reduced the internal pressure of the aneurysm dome and made it suitable for dissection from the surrounding environment (Figures 1,2). Temporary clipping was applied in areas where perforating arteries would be least affected and were suitable for repetitive manipulations. Placing a pilot clip helped in elucidating the relationship of the aneurysm with the surrounding anatomical structures in thorough explorations of the dome, especially in cases of large aneurysms, and minimized the risk of rupture until the final clipping (Figure 3). The active presence of a second surgeon in the room facilitated dynamic retraction and manipulation with a third hand and allowed clip repositioning and placement of multiple clips when necessary (Figure 4). The technical details of these procedures have been discussed in previous studies (19).

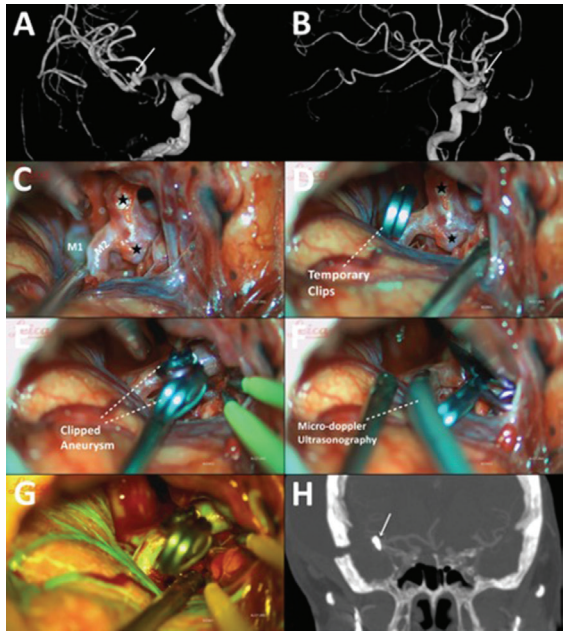

Figure 1. A 71-year-old female patient who underwent surgery due to an aneurysm in the hemorrhaging bifurcation of the right middle cerebral artery (MCA). A,B. Three-dimensional anterior-posterior and lateral images from preoperative digital subtraction angiography showing a saccular aneurysm (arrow) involving both trunci with a small bleb in the right MCA bifurcation, measuring 6×4 mm. C. Image of the aneurysm dome (star) and the right MCA M1 and M2 segments. D. Image of the temporary clip placed on the aneurysm dome and right MCA M1 segment. E. Image of the aneurysm dome being closed with two permanent clips. F. Image of the flow in the aneurysm dome and right MCA branches being explored by micro-Doppler ultrasonography. G. Videoangiography mode image after sodium fluorescein injection showing that the aneurysm dome is not filled. H. Postoperative computed tomography brain angiography image, coronal section, showing the aneurysm clip (arrow), no residual aneurysmal embolization, and no parent artery loss

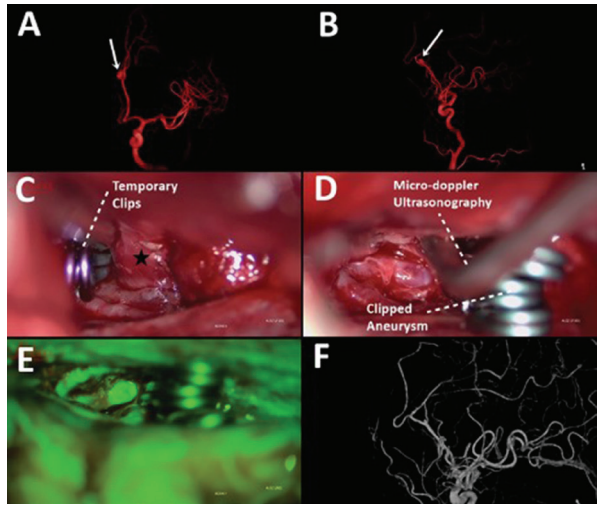

Figure 2. A 55-year-old female patient who underwent surgery due to an aneurysm in the hemorrhaging left pericallosal artery. A,B. Three-dimensional anterior-posterior and lateral images from preoperative digital subtraction angiography (DSA) showing an anterosuperiorly oriented saccular aneurysm with a narrow neck (arrow) in the left pericallosal artery, measuring 6.5×5.2 mm. C. Image of the aneurysm dome (star) and a temporary clip placed proximally to the aneurysm. D. Image of the aneurysm dome being closed with three permanent clips. The distal aneurysm is being explored by micro-Doppler ultrasonography. E. Videoangiography mode image after sodium fluorescein injection showing that the aneurysm dome is not filled. F. Postoperative 3-dimensional DSA image showing millimetric residual aneurysmal filling

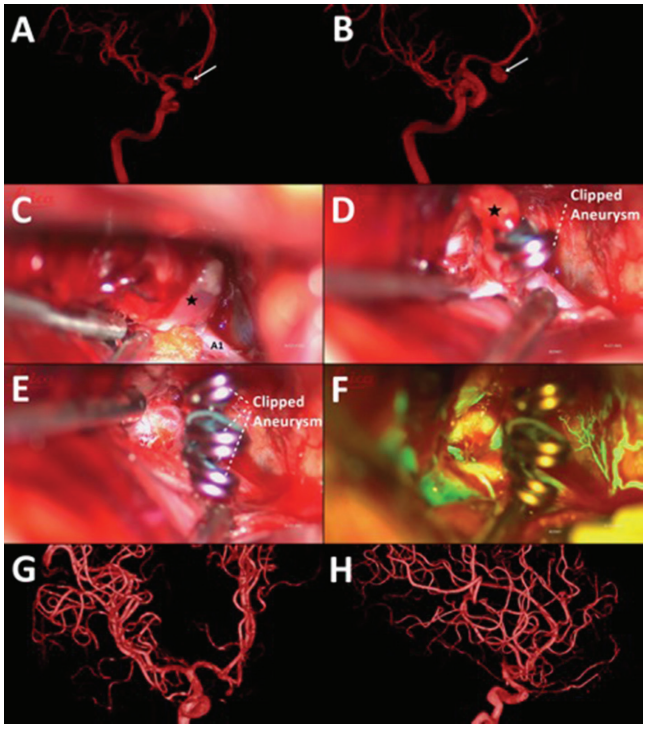

Figure 3. A 30-year-old male patient who underwent surgery due to an artery aneurysm in the hemorrhaging anterior communicating segment (Acom). A,B. Three-dimensional anterior-posterior and lateral images from preoperative digital subtraction angiography (DSA) showing an anteroinferiorly oriented, narrow-necked, irregularly contoured saccular aneurysm (arrow) filling from the right at the Acom level, measuring 8.5×6.1 mm. C. Image of the aneurysm dome (star) and the A1 segment of the right anterior cerebral artery. D. Image of the aneurysm dome (star) and the pilot clip placed on the hemorrhaging component. E. Image of the aneurysm dome being closed with serial clipping. F. Videoangiography mode image after sodium fluorescein injection showing that the aneurysm dome is not filled. G,H. Anterior-posterior and lateral images from postoperative DSA showing no residual aneurysmal filling and no loss of parent arteries

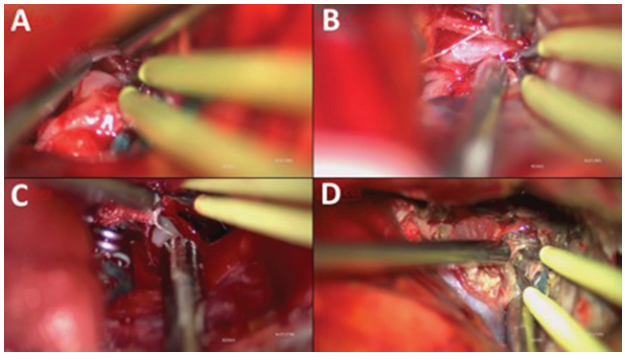

Figure 4. A-D. Images of retraction and aspiration performed in four different cases before aneurysm clipping with the help of the aspirator used by the second surgeon with the third-hand technique

Following the clipping of the aneurysm and ensuring optimal clip positioning via surgical observation and microvascular Doppler sonography (Hadeco Inc., Japan, and Koven Technology Inc., USA), sodium fluorescein videoangiography was performed using the FL560 module of a microscope (Figures 1,2,5). The details of this procedure have been discussed in previous studies (10).

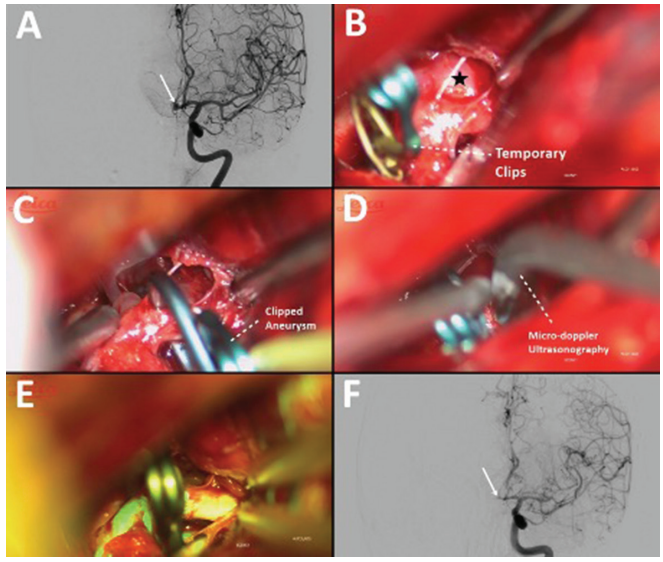

Figure 5. A 65-year-old female patient who underwent surgery due to an artery aneurysm in the hemorrhaging anterior communicating segment (Acom). A. Anterior-posterior and lateral image from preoperative digital subtraction angiography (DSA) showing a right-anterolaterally oriented saccular aneurysm (arrow) with an abnormal border at the Acom level and a narrow neck, involving the left A2 and measuring approximately 5.6×3.5 mm. B. Image of the aneurysm dome (star) and the temporary clip placed on the A1 segment of the left anterior cerebral artery. C. Image of the aneurysm being closed with a single permanent fenestrated clip. D. Image of the flow to the A1 segments of the right and left anterior cerebral artery used to explore the aneurysm dome by micro-Doppler ultrasonography. E. Videoangiography mode image after sodium fluorescein injection showing that the aneurysm dome is not filled. F. Anterior-posterior image from postoperative DSA showing an atrium-shaped residual aneurysmal filling (arrow), measuring 1.2×1 mm.

Postoperative Procedure

In the early postoperative period, all patients were screened using non-contrast brain CT to exclude possible complications secondary to surgery. Contrast brain CT angiography and/or DSA were performed for patients within a few days after the operation to evaluate whether total obliteration of the aneurysm had been achieved. Diffusion-weighted magnetic resonance imaging (DW-MRI) was performed when necessary to confirm the suspicion of delayed cerebral ischemia.

Statistical Analysis

Statistical analyzes were performed using the SPSS software.

CV Prophylaxis and Management

Hyponatremia was aggressively treated in all patients. Hemoglobin levels were maintained above 9-10 g/dL. No long-term epileptic seizure prophylaxis was administered.

All patients admitted to our hospital with a diagnosis of sSAH were administered prophylactic oral nimodipine (6×60 mg) and oral cilostazol (2×100 mg) during the postoperative period. Patients with CV symptoms who had no contraindications underwent single or serial lumbar puncture. Patients who developed delayed cerebral

ischemia and did not have cardiac contraindications were treated for hypotension with inotropes. Patients with progressive conditions who showed no response to medical treatment were treated with intraarterial vasodilators and/or balloon angioplasty after consultations with interventional radiologists (Figure 6).

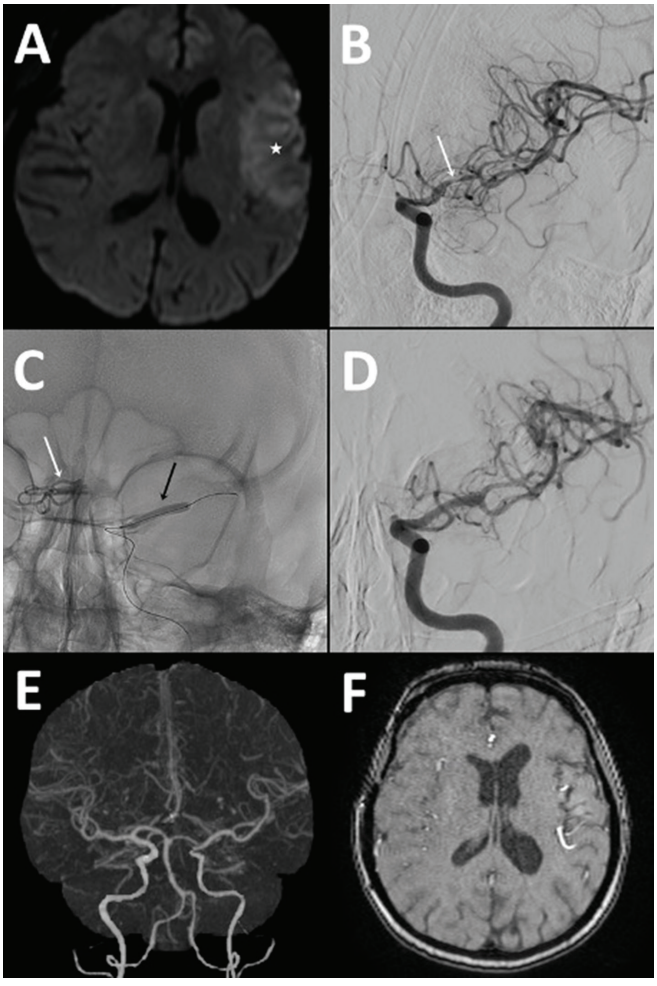

Figure 6. A 50-year-old female patient who underwent surgery due to an artery aneurysm in the hemorrhaging anterior communicating segment (Acom). A. Diffusion magnetic resonance imaging (MRI) was performed for the patient on the postoperative sixth day after the development of aphasia and paresis in the right upper limb. Image of an acute ischemic area (star) causing diffusion restriction in the watershed area of the left middle cerebral artery (MCA) in the left parietal region. B. Anterior-posterior image from preoperative digital subtraction angiography showing significant vasospasm in the left MCA (arrow) and slowed flow in the distal branches. Upon this finding, 2 mg of intraarterial nimodipine was administered to the patient. C. Upon the patient showing no response to nimodipine, balloon angioplasty was performed on the left MCA M1 segment with a compliant balloon of 4×20 mm (black arrow). Image shows clip material (white arrow) in the Acom arterial area. D. Anterior-posterior control image showing that the vasospasm was completely eliminated and the flow in the distal branches returned to normal. The patient's aphasia and paresis of the right upper extremity improved. E. Three-dimensional anterior-posterior computed tomography brain angiography image taken 1 year later showing that the left MCA and its branches have normal width and correct location. F. Axial section of MRI angiography performed 1 year later showing no infarct areas

RESULTS

The average age of the 107 aSAH patients treated with microsurgical clipping was 50.4 years (range: 29-78 years). Of the patients included in the study, 52 were female (48%) and 55 were male (52%). The main complaints of these patients upon admission to the hospital are summarized in Table 1. Headache was a significantly common complaint (75.8%) at admission. A total of 107 operations were performed for the included patients, and 117 aneurysms were clipped throughout the 107 operations (Table 2). The average follow-up time of the patients was 13.8 months or 414 days (range: 30-892 days).

Multiple aneurysms were detected in 28 (26.1%) patients with aSAH who were treated with microsurgical clipping. Ten (9.3%) patients with more than one aneurysm underwent multiple aneurysm clippings in the same session. Four (3.7%) patients required a second intervention, and their treatments were planned with the interventional radiology and neurosurgery clinics. No second interventions were planned for the aneurysms of 14 (13%) patients because of the absence of treatment indications, and these cases were followed radiologically. The Glasgow coma scale (GCS) scores of aSAH patients are presented in Table 3. It was found that approximately 72.9% of the patients had GCS scores of 14 or 15.

The clinical classifications of patients with aSAH can be determined using the WFNS classifications and H/HS scale, while their radiological classifications can be determined using mFS scores. The classification information of the 107 patients included in this study is presented in Table 4.

Among our cohort of patients with aSAH, 17 (15.8%) showed signs of hydrocephalus at admission to the hospital and required external ventricular drainage, whereas only 11 (10.2%) underwent ventriculoperitoneal (VP) shunting. In addition, 2 patients (1.8%) who did not show signs of hydrocephalus at admission to the hospital but showed signs of hydrocephalus during long-term follow-up required permanent cerebrospinal fluid drainage systems. A total of 13 (12%) patients required VP shunting.

Seven (6.5%) of the 107 patients in our cohort developed repeat bleeding. Three patients developed repeated bleeding before admission to our clinic based on epicenter non-contrast brain CT comparisons, whereas four patients developed repeated bleeding within the first 12 hours (h) after admission.

CV was detected in 36 (33.6%) patients. Twenty-five (23.3%) patients were diagnosed with delayed cerebral ischemia using DW-MRI. Lumbar puncture was performed

in 28 patients. Sixteen patients underwent intraarterial nimodipine administration and/or balloon angioplasty performed by interventional radiologists.

Morbidity

At the end of an average follow-up period of 13.8 months, 82.3% of aSAH patients treated with microsurgical clipping had no disabilities or were slightly disabled (mRS: 0-2), whereas 11.2% were severely disabled (mRS: 3-5). The mRS scores of the patients are presented in Table 5. Comparisons of mRS scores with WFNS and H/HS scores are presented in Tables 6 and 7, respectively.

Mortality

Seven (6.5%) patients died, thus having an mRS score of 6 (exitus). Three patients died because of complications that developed because of rebleeding, which occurred shortly after the patients were admitted to our center. Three patients had stable postoperative conditions for at least 24 h and then developed delayed cerebral ischemia, which was confirmed via DW-MRI and CT. CV was confirmed via DSA. In the applied medical and invasive treatment protocols for CV, which included intraarterial nimodipine and balloon angioplasty, CV complications resulted in death. A patient who had a GCS score of 7 at the start of the operation did not achieve any clinical progress in the intensive care unit (ICU) follow-up after the operation and died because of hemodynamic instability and morbidities developing during follow-up. Comparisons of the mRS scores of the patients with their WFNS and H/HS scores are presented in Tables 6 and 7.

Table 1. Complaints at the time of application

Complaints	Value	Percent
Headache	81	75.8%
Loss of consciousness	17	15.8%
Seizure	3	2.8%
Focal neurological deficit	6	5.6%
Total	107	100

Table 2. Aneurysm localizations

Aneurysms	Value	Percent
Anterior communicating artery	50	41.9%
Middle cerebral artery bifurcation/trifurcation	30	25.6%
Middle cerebral artery-M1 branches	4	2.5%
Middle cerebral artery-M2 branches	3	3.4%
Posterior communicating and anterior choroidal artery	20	17.2%
Internal carotid artery-bifurcation	5	4.3%
Anterior cerebral artery-A1 branches	2	1.7%
Anterior cerebral artery-A2 branches	3	3.4%
Total	117	100%

Surgical Complications

Residual aneurysms were detected in 5 cases (4.6%) via postoperative DSA. One of these patients was followed without intervention because the size of the residual aneurysm was 1-2 mm. The other four patients underwent endovascular treatments (flow-diverting stent or coil + flow-diverting stent) instead of repeated microsurgical interventions.

Table 3. Glasgow coma scale of aSAH patients

GCS score	Amount of patients	Percent
3	2	1.8%
4	2	1.8%
5	2	1.8%
6	1	0.9%
7	3	2.8%
8	4	3.7%
10	2	1.8%
11	1	0.9%
12	3	2.8%
13	9	8.5%
14	32	30%
15	46	43.2%
Total	107	100

GCS: Glasgow coma scale, aSAH: Aneurysmal subarachnoid hemorrhage

Table 4. International subarachnoid hemorrhage

	Classifications					
	WFNS grade		Hunt and Hess grade		M. Fisher grade	
Grade	n	%	n	%	n	%
I	46	42.9	40	37.4	37	34.6
Ia	-	-	1	0.9	-	-
II	36	33.6	37	34.6	2	1.8
III	5	4.7	13	12.2	47	43.9
IV	13	12.2	10	9.3	21	19.7
V	7	6.6	6	5.6	-	-
Total	107	100	107	100	107	100

WFNS: World Federation of Neurological Surgeons

Parent or perforating artery occlusion occurred in 6 (5.6%) patients secondary to surgery. The infarction areas detected in 3 patients were asymptomatic or had temporary symptoms. In 3 cases, permanent neurological deficits occurred. Although the aneurysm of the first patient occurred in the bifurcation of the right internal carotid artery, the right choroidal artery was observed during the operation, and the temporary clip was placed distally to the choroidal segment, 1/5 left-sided hemiparesis occurred due to right choroidal artery infarction that developed in the postoperative period. At the end of the follow-up period, the paresis of this patient improved by up to 4/5 in left lower muscle strength and 3/5 in left upper muscle strength because of physical therapy. The second patient had a widespread left large middle cerebral artery infarction, which caused right-sided hemiplegia and aphasia. After the fetal-type left posterior communicating artery aneurysm of the third patient was clipped, fragmentary infarction was observed in the left posterior cerebral artery watershed area, and the patient experienced 4/5 right-sided hemiparesis.

Rhinorrhea due to a defect opening to the sphenoid sinus occurred in one patient in the postoperative period, and the skull base of that patient was treated in a second operation. The patient did not have any further complaints during the follow-up period. Another patient had tension pneumocephalus due to a frontal sinus defect, and the skull base of that patient was treated in a second operation. One other patient underwent a second operation because of an

Table 5. Modify Rankin scale of aSAH patients

	n	%	%
0	76	71.1	
1	10	9.4	82.3
2	2	1.8	
3	3	2.8	
4	3	2.8	11.2
5	6	5.6	
6	7	6.5	6.5
Total	107	100	100

aSAH: Aneurysmal subarachnoid hemorrhage

Table 6. International subarachnoid hemorrhage classifications

	WFNS grade		mRS 0-1-2		mRS 3-4-5		mRS 6	
Grade	n	%	n	%	n	%	n	%
I	46	42.9	42	91.3	4	8.7	0	0
II	36	33.6	33	91.6	2	5.6	1	2.8
III	5	4.7	4	80	0	0	1	20
IV	13	12.2	5	38.5	3	23	5	38.5
V	7	6.6	2	28.5	5	71.5	0	0
Total	107	100	86	100	14	100	7	100

WFNS: World Federation of Neurological Surgeons, mRS: Modified Rankin scale

Table 7. International subarachnoid hemorrhage classifications

	H/HS grade		mRS 0-1-2		mRS 3-4-5		mRS 6	
Grade	n	%	n	%	n	%	n	%
I	40	37.4	36	90	4	10	0	0
Ia	1	0.9	1	100	0	0	0	0
II	37	34.6	35	95	1	2.5	1	2.5
III	13	12.2	9	70	1	7	3	23
IV	10	9.3	4	40	4	40	2	20
V	6	5.6	1	16.5	4	67	1	16.5
Total	107	100	86		14		7	

mRS: Modified Rankin scale, H/HS: Hunt/Hess scale

epidural hematoma detected in a postoperative brain CT scan. All complications are presented in Table 8.

Table 8. Surgical complications of aSAH patients

Complications	Value	Percent
Infarct (mean braches and perforans)	6	5.6%
Cerebrospinal fluid leaks	1	0.9%
Skin wound problem	2	1.8%
Epidural hematom	1	0.9%
Tension pneumocephalus	1	0.9%
Total	11	10.2%

aSAH: Aneurysmal subarachnoid hemorrhage

DISCUSSION

This study provides data on the clinical profiles, management, and outcomes of patients admitted with sSAH diagnoses to a hospital that serves as a reference center, located in a large metropolis with a population of approximately 8-10 million. Our clinic has established a rapid referral chain in coordination with emergency transport units. The treatment of admitted patients is planned as either surgical or neurovascular intervention according to the clinical condition of the patient and the location of the detected aneurysm. Because almost all patients in the large region for which the clinic provides treatment services are referred to our hospital regardless of good or poor condition, it is thought that this study is capable of accurately reflecting the morbidity and mortality rates associated with the treatment of aSAH through microsurgical clipping. Thus, it is believed that this study will make a valuable contribution to the literature.

With the exception of Japan and Finland, where the figures are doubled because of genetic factors, the overall incidence of aSAH has remained at a stable level of 9/100,000 per year worldwide (20,21). sSAH most often occurs in the age range of 40-60 years, with an average patient age of 50. It has been observed that the incidence of sSAH increases with age (22). Headaches constitute 2% of all complaints among all patients at first admission to emergency departments, and 1-3% of patients who complain of headaches are diagnosed with sSAH (23). Because headache is a common complaint, certain characteristics should be considered to avoid overlooking the possibility of sSAH, such as sudden and severe headaches with comorbid neurological deficits or patients over the age of 40. The main complaint of 75.8% of the patients included in this study was headache, and the average age of the patients was 50.4 years (range: 29-78 years).

The most important factor determining the prognosis of patients with aSAH is the initial condition of the patient. In this context, the GCS, WFNS, and H/HS scales are most frequently used for the classification of patients with aSAH (7,24,25). mFS, on the other hand, is used to predict CV (17). In this study, mortality and morbidity results based on mRS scores were compared with WFNS and H/HS scores.

The 2002 ISAT study (26) evaluating microsurgical clip treatment results reported that 36.4% of patients who underwent the procedure had mRS scores of 3-6 and 8.3% of them had mRS scores of 6 (exitus) at the second month after the procedure, while 30.6% of patients had mRS scores of 3-6 and 10.1% had mRS scores of 6 (exitus) in the first year following the procedure. An extensive meta-analysis revealed that 15% of patients who underwent the procedure had mRS scores of 6 (exitus), whereas 30.9% of them had mRS scores of 3-6 (27). The same meta-analysis showed that the complication rate of microsurgical clipping operations was 10.8%. In the present study, it was determined that 17.7% of patients who underwent the procedure had mRS scores of 3-6 and 6.5% had mRS scores of 6 at the end of an average follow-up period of 13.8 months. The surgical complication rate determined in this study was 10.2%. The lower mortality and morbidity rates of the present study compared with the literature may be explained by the fact that posterior circulation aneurysms were not included in this study and the study included fewer patients compared with the aforementioned series.

It was observed that a center with fewer than 10 annual sSAH patient admissions had a significantly lower mortality rate than a center with more than 35 annual sSAH patient admissions (28). However, multidisciplinary centers with neurointensive care units and experienced endovascular and vascular surgical teams that accept a high number of cases are recommended for patients with sSAH (7,25,29). During this study, approximately 130 sSAH patients were admitted to our center annually, and approximately 50 aSAH patients underwent microsurgical clipping. High patient admission rates help not only the surgical team but also branch practitioners such as anesthesiologists or endovascular experts, physicians, and non-physician medical personnel working in units such as in-patient departments and ICUs gain experience and contribute to improved morbidity and mortality rates.

A multidisciplinary approach assisted by an endovascular team is important for treating aSAH (7,24). The technical capabilities of the center and the experience of the

surgical team are the foremost factors that determine the treatment methods for aneurysms (29). In addition to factors such as the location, structure, and width of the aneurysm and the narrowness of the aneurysm neck, factors such as the patient's age, general condition, and presence of intracerebral hematoma are influential in the selection of aneurysm treatment methods (7,24,29). In our clinic, the indication for microsurgical clipping is decided on according to general principles with the deliberation of a council that includes an endovascular team. In centers with high caseloads, it is important for both the surgical and vascular teams to evaluate patients and plan together according to their schedules to be able to treat patients with the most appropriate decisions in the shortest possible time.

Rebleeding is one of the most important complications occurring among patients with aSAH in the period leading up to treatment (30). It tends to occur within the first 3 days after aSAH, and its incidence rate is approximately 13% on average (31). The rate of incidence of rebleeding is 3-4% within the first 24 h, and it most commonly occurs within 2-12 h (22). Rebleeding is a complication that significantly increases the risk of mortality and morbidity; the mortality and morbidity rates of patients who develop rebleeding may reach up to 80% (12,13). In the literature, it has been reported that delays in hospital admission and diagnosis vary by geographical region, but evidence suggests that these delays worsen the prognosis of patients (2). The timing of treating an aneurysm is important because of the risk of rebleeding. The consensus in the literature holds that the final treatment of patients should be planned as soon as possible within 72 h after the first hemorrhage, taking into account the technical capabilities of the center and vascular teams and the patient's condition (22,23,25,29,32). Furthermore, centers that perform extremely early surgery within 24 h have shared results that can be considered significantly positive (33,34). In this study, rebleeding was observed in 7 of 107 patients (6.5%) and 2 of those 7 patients died. Most patients who developed rebleeding in this study had that complication before reaching our center or at a time early enough to make treating the aneurysm impossible. In our center, most patients undergo final treatment within less than 24 h and a maximum of 72 h.

Approximately 70% of aSAH patients develop CV, and approximately 30% of these patients develop symptomatic CV or delayed cerebral ischemia observed in imaging. Although compounds are utilized against CV and delayed cerebral ischemia, effective medical treatments are still being researched (11). Hypervolemia, hemodilution, and hypertension, known as 3-H treatment, are no longer recommended treatment options for this condition. Induced hypertension is indicated for symptomatic patients, but its use may be limited by the patient's cardiac condition (29,35). Oral nimodipine is a compound whose efficacy has been proven in randomized controlled trials (24,25,29). Cilostazol is also a promising compound whose effectiveness against symptomatic and radiological CV has been demonstrated (36). In addition, cisternal irrigation and lumbar drainage are among the methods that have positive clinical effects on CV outcomes. Although endovascular treatment methods, including intraarterial vasodilator compound injections and balloon angioplasty, are not recommended as prophylactic treatments for CV, they produce positive results in patients with resistant clinical conditions (37). In this series, all patients were administered prophylactic oral nimodipine and cilostazol. Despite prophylactic treatment, symptomatic vasospasms were observed in 33.6% of the patients, which is a rate similar to that reported in the literature. Patients who developed CV despite prophylactic treatment were treated incrementally with lumbar puncture, induced hypertension, and endovascular treatments, such as intraarterial vasodilators and/or balloon angioplasty, in the event that they did not respond to other treatments. Hydrocephalus and hyponatremia are among the complications of sSAH. They are associated with poor clinical outcomes and should be promptly treated (29,38-40).

In the literature, the rate of parent or perforating artery occlusion secondary to surgery has been reported to be 0.3-12%. In an extensive series, the rate of residues in aneurysm domes was reported to be 5.9% (41,42). It has also been reported in the literature that the use of intraoperative auxiliary techniques such as videoangiography and microvascular Doppler sonography reduces mortality and morbidity by protecting the perforating and parent arteries and ensuring the complete closure of the aneurysm dome, which are the main aims of vascular surgery (8-10,19). Sodium fluorescein videoangiography and microvascular Doppler sonography were used in this study. The parent or perforating artery occlusion rate was 5.6%, and the residual rate in the aneurysm dome was 4.6%.

There are currently two main treatment methods for aSAH: endovascular treatment and microsurgical clipping. Discussing all possible treatment methods and their results within a single population would allow better elucidation of aSAH treatment options. However, this study has only presented the results of patients who underwent microsurgical clipping. The fact that the follow-up procedures and the results achieved by the endovascular team were not discussed is another limitation of this study.

CONCLUSION

The occurrence of aSAH continues to challenge the healthcare system in Türkiye and in other developing countries. Early detection strategies, fully equipped third-line hospitals, and effective referral systems are necessary to treat aSAH patients in a timely manner. Multidisciplinary approaches applied by experienced endovascular and neurosurgical teams are important for better understanding and management of this disease. sSAH should be considered within the framework of all aspects of its complicated management, including diagnosis, treatment, and the possibility of rebleeding or CV.

ETHICS

Ethics Committee Approval: Approval for the study from the Ethics Committee of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital (decision no: 358, date: 16.08.2023) obtained.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: B.E., E.A., L.Ş.P., Concept: B.E., S.D., O.B., O.H., F.Ş., L.Ş.P., Design: E.A., Y.K., S.D., O.B., Data Collection or Processing: B.E., E.A., Y.K., O.H., F.Ş., Analysis or Interpretation: B.E., O.B., L.Ş.P., Literature Search: B.E., Y.K., S.D., O.H., F.Ş., Writing: B.E., E.A., Y.K., S.D., O.B., O.H., F.Ş., L.Ş.P.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol 2003;2:43-53.
2. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurol 2009;8:635-42.
3. Hop JW, Rinkel GJ, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. Stroke 1997;28:660-4.
4. Fogelholm R, Hernesniemi J, Vapalahti M. Impact of early surgery on outcome after aneurysmal subarachnoid hemorrhage. A population-based study. Stroke 1993;24:1649-54.
5. Cahill J, Zhang JH. Subarachnoid hemorrhage: is it time for a new direction? Stroke 2009;40(3 Suppl):S86-7.
6. Sobey CG, Faraci FM. Subarachnoid haemorrhage: what happens to the cerebral arteries? Clin Exp Pharmacol Physiol 1998;25:867-76.
7. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke 2012;43:1711-37.
8. Fischer G, Stadie A, Oertel JM. Near-infrared indocyanine green videoangiography versus microvascular Doppler sonography in aneurysm surgery. Acta Neurochir (Wien) 2010;152:1519-25.
9. Özgiray E, Aktüre E, Patel N, Baggott C, Bozkurt M, Niemann D, et al. How reliable and accurate is indocyanine green video angiography in the evaluation of aneurysm obliteration? Clin Neurol Neurosurg 2013;115:870-8.
10. Küçükyürük B, Korkmaz TŞ, Nemayire K, Özlen F, Kafadar AM, Akar Z, Kaynar MY, et al. Intraoperative Fluorescein Sodium Videoangiography in Intracranial Aneurysm Surgery. World Neurosurg 2021;147:e444-52.
11. Smetana KS, Buschur PL, Owusu-Guha J, May CC. Pharmacologic Management of Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage. Crit Care Nurs Q 2020;43:138-56.
12. Roos YB, de Haan RJ, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M. Complications and outcome in patients with aneurysmal subarachnoid haemorrhage: a prospective hospital based cohort study in the Netherlands. J Neurol Neurosurg Psychiatry 2000;68:337-41.
13. Chung DY, Abdalkader M, Nguyen TN. Aneurysmal Subarachnoid Hemorrhage. Neurol Clin 2021;39:419-42.
14. Kassell NF, Boarini DJ, Adams HP Jr, Sahs AL, Graf CJ, Torner JC, et al. Overall management of ruptured aneurysm: comparison of early and late operation. Neurosurgery 1981;9:120-8.
15. Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale. J Neurosurg 1988;68:985-6.
16. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg 1968;28:14-20.
17. Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Copeland D, et al. Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. Stroke 2001;32:2012-20.
18. Lindley R, Waddell F, Livingstone M, Sandercock P, Dennis M, Slattery J, et al. Can simple questions assess outcomes after stroke? Cerebrovasc Dis 1994;4:314–24.
19. Erkan B, Akpınar E, Kılıç Y, Demir S, Barut O, Postalcı LŞ. Single-centre Microsurgery Treatment Methods for Unruptured Intracranial Aneurysms of the Anterior Circulation and Results. Bagcilar Med Bull 2023;8:68-77.
20. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;8:355-69.
21. Hughes JD, Bond KM, Mekary RA, Dewan MC, Rattani A, Baticulon R, et al. Estimating the Global Incidence of Aneurysmal Subarachnoid Hemorrhage: A Systematic Review for Central Nervous System Vascular Lesions and Meta-Analysis of Ruptured Aneurysms. World Neurosurg 2018;115:430-47.
22. Bederson JB, Connolly ES Jr, Batjer HH, Dacey RG, Dion JE, Diringer MN, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 2009;40:994-1025.
23. Perry JJ, Stiell IG, Sivilotti ML, Bullard MJ, Hohl CM, Sutherland J, et al. Clinical decision rules to rule out subarachnoid hemorrhage for acute headache. JAMA 2013;310:1248-55.
24. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis 2013;35:93-112.
25. Committee for Guidelines for Management of Aneurysmal Subarachnoid Hemorrhage, Japanese Society on Surgery for Cerebral Stroke. Evidence-based guidelines for the management of aneurysmal subarachnoid hemorrhage. English Edition. Neurol Med Chir (Tokyo) 2012;52:355-429.

26. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet 2005;366:809-17.
27. Peng C, Diao YH, Cai SF, Yang XY. Endovascular coiling versus microsurgical clipping for ruptured intracranial aneurysms: a meta-analysis and systematic review. Chin Neurosurg J 2022:25;8:17.
28. Cross DT 3rd, Tirschwell DL, Clark MA, Tuden D, Derdeyn CP, Moran CJ, et al. Mortality rates after subarachnoid hemorrhage: variations according to hospital case volume in 18 states. J Neurosurg 2003;99:810-7.
29. Cho WS, Kim JE, Park SQ, Ko JK, Kim DW, Park JC, et al. Korean Clinical Practice Guidelines for Aneurysmal Subarachnoid Hemorrhage. J Korean Neurosurg Soc 2018;61:127-66.
30. Stienen MN, Germans M, Burkhardt JK, Neidert MC, Fung C, Bervini D, et al. Predictors of In-Hospital Death After Aneurysmal Subarachnoid Hemorrhage: Analysis of a Nationwide Database (Swiss SOS [Swiss Study on Aneurysmal Subarachnoid Hemorrhage]) Stroke. 2018;49:333-40.
31. Tang C, Zhang TS, Zhou LF. Risk factors for rebleeding of aneurysmal subarachnoid hemorrhage: a meta-analysis. PLoS One 2014;9:e99536.
32. de Gans K, Nieuwkamp DJ, Rinkel GJ, Algra A. Timing of aneurysm surgery in subarachnoid hemorrhage: a systematic review of the literature. Neurosurgery 2002;50:336-40.
33. Pan JW, Zhan RY, Wen L, Tong Y, Wan S, Zhou YY. Ultra-early surgery for poor-grade intracranial aneurysmal subarachnoid hemorrhage: a preliminary study. Yonsei Med J 2009;50:521-4.
34. Laidlaw JD, Siu KH. Ultra-early surgery for aneurysmal subarachnoid hemorrhage: outcomes for a consecutive series of 391 patients not selected by grade or age. J Neurosurg 2002;97:250-8.
35. Neifert SN, Chapman EK, Martini ML, Shuman WH, Schupper AJ, Oermann EK, et al. Aneurysmal Subarachnoid Hemorrhage: the Last Decade. Transl Stroke Res 2021;12:428-46.
36. Bohara S, Garg K, Singh Rajpal PM, Kasliwal M. Role of Cilostazol in Prevention of Vasospasm After Aneurysmal Subarachnoid Hemorrhage-A Systematic Review, Meta-Analysis, and Trial Sequential Analysis. World Neurosurg 2021;150:161-70.
37. Li K, Barras CD, Chandra RV, Kok HK, Maingard JT, Carter NS, et al. A Review of the Management of Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage. World Neurosurg 2019;126:513-27.
38. Qureshi AI, Suri MF, Sung GY, Straw RN, Yahia AM, Saad M, et al. Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2002;50:749-55.
39. Levine JM. Critical care management of subarachnoid hemorrhage. Curr Treat Options Neurol 2009;11:126-36.
40. Dorai Z, Hynan LS, Kopitnik TA, Samson D. Factors related to hydrocephalus after aneurysmal subarachnoid hemorrhage. Neurosurgery 2003;52:763-9.
41. Origitano TC, Schwartz K, Anderson D, Azar-Kia B, Reichman OH. Optimal clip application and intraoperative angiography for intracranial aneurysms. Surg Neurol 1999;51:117-24.
42. Sindou M, Acevedo JC, Turjman F. Aneurysmal remnants after microsurgical clipping: classification and results from a prospective angiographic study (in a consecutive series of 305 operated intracranial aneurysms). Acta Neurochir (Wien) 1998;140:1153-9.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:339-351
DOI: 10.4274/BMJ.galenos.2023.2023.6-7

Research

Diagnostic Approach to Pulmonary Embolism in Patients with COVID-19 Pneumonia: A Single-center Study

COVİD-19 Pnömonili Hastalarda Pulmoner Emboliye Tanısal Yaklaşım: Tek Merkezli Bir Çalışma

Işıl Kibar Akıllı[1], Müge Bilge[2]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pulmonary Disease, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye

ABSTRACT

Objective: During coronavirus disease-2019 (COVID-19), numerous studies have delineated an increased risk of developing pulmonary embolism (PE). The aim of this study was to determine the prevalence of PE diagnosed on computed tomography (CT) pulmonary angiography (CTPA) in patients with COVID-19 pneumonia. To evaluate the clinical features and outcomes of PE in these individuals. In addition, the use of D-dimer and predictive scores for the diagnosis of PE in COVID-19 were assessed.

Methods: All patients with COVID-19 pneumonia who underwent CTPA for suspected PE were retrospectively reviewed. Data of all clinical, laboratory, and CTPA images were obtained from electronic medical records. CTPA images were assessed for PE presence, PE distribution, and extent of lung involvement. The severity of lung involvement was graded by chest CT. D-dimer levels within 24 hours from CTPA were obtained. Clinical characteristics and laboratory data were analyzed and compared between patients with and without PE.

Results: PE was detected in 96 of 220 (43.63%) patients who underwent CTPA for suspected PE. Women had a higher rate of PE ($p<0.05$). D-dimer values were significantly higher ($p=0.001$) in PE patients, and the median value in the PE group was 5.6 µg FEU/mL (range 2-5.9). A D-dimer cut-off value of 3.95 µg FEU/mL provides a sensitivity of 0.64 and specificity of 0.69. Area under the curve of the receiver operating characteristic curve is 0.626 [95% confidence interval (CI) = 0.550-0.703. $p=0.001$]. PE cases had significantly higher severe CT lung parenchymal involvement compared with non-PE ($p<0.05$). PE was seen in major vessels in 31.25% (30 cases) and in minor vessels 34.37% (33 cases). Backward logistic regression analysis revealed that female sex and hemoptysis increased the risk of PE by 2.643 and 10.6, respectively ($p<0.05$ for both). The Wells score three-level model was similar in the PE and non-PE group ($p>0.05$). However, only 16.7% of patients with PE had a Wells score more than 4 points ($p<0.05$).

Conclusion: We observed that almost half of the COVID-19 pneumonia patients assessed following contrast media administration had PE on CT. The Wells score used in the general population was not helpful in the diagnosis of PE, and the pulmonary embolism severity index score was unreliable in predicting the mortality risk of PE in these patients. Higher D-dimer values may detect COVID-19-related PE. These findings indicate that CTPA could be more widely used when assessing individuals with COVID-19 pneumonia, particularly in those with elevation of D-dimer and presence of hemoptysis.

Keywords: Pulmonary embolism, COVID-19 pneumonia, D-dimer, computed tomography pulmonary angiography

ÖZ

Amaç: Çok sayıda çalışma koronavirüs hastalığı-2019 (COVİD-19) pandemisi sırasında pulmoner emboli (PE) gelişme riskinin arttığını bildirmiştir. Bu çalışmanın amacı, COVİD-19 pnömonisi olan olgularda bilgisayarlı tomografi pulmoner anjiyografi (BTPA) ile PE prevalansını belirlemek, bu olgularda PE'nin klinik özelliklerini ve sonuçlarını değerlendirmektir. Bununla birlikte COVİD-19 ile ilişkili PE tanısında D-dimer ve prediktif skorların kullanımı değerlendirilmiştir.

Gereç ve Yöntem: PE şüphesi ile BTPA yapılmış tüm COVİD-19 pnömonisi olguları retrospektif olarak incelendi. Tüm klinik, laboratuvar ve BTPA görüntülerinin verileri elektronik tıbbi kayıtlardan elde edildi. BTPA görüntüleri PE varlığı, PE dağılımı ve akciğer parankim tutulumu açısından değerlendirildi. BTPA'nın 24 saati içindeki D-dimer düzeyleri elde edildi. PE saptanan ve saptanmayan olguların klinik özellikleri ve laboratuvar verileri analiz edildi ve karşılaştırıldı.

Address for Correspondence: Işıl Kibar Akıllı, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pulmonary Disease, İstanbul, Türkiye
Phone: +90 0212 414 71 71 E-mail: isilkibar@yahoo.com ORCID ID: orcid.org/0000-0002-4969-4512

Cite as: Kibar Akıllı I, Bilge M. Diagnostic Approach to Pulmonary Embolism in Patients with COVID-19 Pneumonia: A Single-center Study. Med J Bakirkoy 2023;19:339-351

Received: 09.07.2023
Accepted: 14.09.2023

Bulgular: BTPA yapılan 220 olgunun 96'sında (%43,63) PE saptandı. Kadın cinsiyette PE oranı yüksek bulundu (p<0,05). PE olgularında D-dimer değerleri daha yüksekti (p=0,001); bu olgularda D-dimer medyan değeri 5,6 µg FEU/mL (2-5,9) bulundu. 3,95 µg FEU/mL D-dimer cut-off değeri ile 0,64 sensitivite ve 0,69 spesifite saptandı. PE olgularında BTPA'da akciğer parankim tutulumunun daha ağır olduğu görüldü (p<0,05). PE olgularında majör damar tutulumu %31,25 (30 olgu) ve minör damar tutulumu %34,37 (33 olgu) olarak saptandı. Regresyon analizi ile hemoptizi varlığının 10,6 kat ve kadın cinsiyetin 2,64 kat artmış PE riski ile birlikte olduğu bulundu. Wells skoru üçlü sınıflama modeli açısından iki grup arasında farklılık saptanmadı (p>0,05). PE olgularının sadece %16,7'sinde Wells skoru 4 puanın üzerinde bulundu (p<0,05).

Sonuç: BTPA ile değerlendirilen COVİD-19 pnömoni olgularının yaklaşık yarısında PE geliştiğini gözlemledik. COVİD-19 ilişkili PE olgularında, genel popülasyonda PE tanısını öngermede kullanılan Wells skoru ve PE mortalite riskini öngörmede kullanılan pulmoner emboli şiddet indeksi skorun güvenilir olmadığı, yüksek D-dimer değerlerinin bu olgularda tanıya yardımcı olabileceği saptandı. Bu bulgular COVİD-19 pnömonisi olgularını değerlendirirken, özellikle belirgin D-dimer yüksekliği ve hemoptizi varlığında BTPA'nın daha yaygın olarak kullanılması gerektiğini düşündürmektedir.

Anahtar Kelimeler: Pulmoner emboli, COVİD-19 pnömonisi, D-dimer, bilgisayarlı tomografi pulmoner anjiyografi

INTRODUCTION

Coronavirus disease-2019 (COVID-19) has been identified as a thrombogenic virus with an increased incidence of pulmonary embolism (PE) and other venous thromboembolic events, resulting in an increase in mortality (1). It has been reported that the incidence of PE in COVID-19 cases is higher than that in influenza and community-acquired pneumonia cases (2). Studies on this subject have reported that the incidence of PE in COVID-19 cases is 10-25% in patients hospitalized in the general ward and 23.4-50% in patients treated in the intensive care unit (ICU) (1-3). As a contradictory finding; the incidence of deep vein thrombosis (DVT) was 14.8% in hospitalized patients with COVID-19, and surprisingly, more than half of COVID-19 patients with PE had no DVT (1). Virchow's triad consists of three components which are reduced blood flow, endothelial damage, and hypercoagulability that leads to increased thromboembolism. Hypercoagulability in COVID-19 emerges due to endothelial injury in all organs, which is accompanied by increases in ferritin, C-reactive protein, D-dimer, fibrinogen, and proinflammatory cytokines, including interleukin-6 (4).

In the setting of COVID-19-related venous thromboembolism (VTE); activation of macrophages, endothelial dysfunction, hyperinflammation, disseminated intravascular coagulation, platelet dysfunction, and *in situ* thrombosis are thought to be involved in the pathogenesis. This condition is called microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (5,6). D-dimer elevation, thrombocytopenia, and prolonged prothrombin time have been reported as coagulation disorders accompanying worse prognosis in COVID-19 cases. D-dimer measurements may contribute to the diagnosis of PE in patients with COVID-19, but an absolute diagnostic threshold value has not yet been determined (7). Clinical pre-test probability criteria such as the Wells score recommended by clinical practice guidelines to predict the diagnosis of PE and the pulmonary embolism severity index (PESI) used to predict PE mortality are unreliable in COVID-19 patients (8-11). Definitions of Wells and PESI scores are given in tables Supplementary Table S1 and S2.

In our study, PE clinical, imaging [computed tomography pulmonary angiogram (CTPA)], laboratory features, and pulmonary distribution were examined in COVID-19 pneumonia cases who underwent CTPA. The aim of this retrospective study was to determine the prevalence of PE diagnosed on CTPA, the distribution of PE, and the severity of chest CT involvement in patients with COVID-19 pneumonia. The usefulness of the D-dimer levels, Wells' criteria, and PESI scale in the diagnosis and prognosis of PE in these individuals was another goal of our study.

METHODS

This retrospective, cross-sectional, single-center study was conducted at the Department of COVID-19 Clinic, Prof. Dr. Murat Dilmener Emergency Hospital, İstanbul, Türkiye, a tertiary pandemic hospital, from June 1, 2021 to 31 December 2021. All consecutive adult (>18 years) hospitalized patients who were diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia by real-time polymerase chain reaction testing and also underwent CTPA imaging for PE within the given time period were searched in the hospital electronic registry system. Patients with no radiological involvement, incomplete clinical and laboratory data were excluded from the study. Another criterion for exclusion was pregnancy. After exclusion, 220 patients (older than 18 years) were included in the study.

The following data were retrospectively extracted from the database of the patient management system of the Department of COVID-19 Clinic, Prof. Dr. Murat Dilmener Emergency Hospital, İstanbul, Türkiye: demographic (age, sex), clinical (comorbidities, pharmacological treatment before and during hospitalization, time between symptoms

onset and hospitalization, time between symptoms onset to CTPA, time between admission and CTPA, the length of hospitalization days), laboratory (D-dimer, PRO-BNP, and high-sensitivity troponin T/hs-TnT), CTPA data, clinical outcomes (death, discharge or ICU admission), and treatment. The reasons patients had been sent for CTPA were obtained from the electronic medical records as an elevated D-dimer level or accompanying symptoms, including chest pain, hemoptysis, dyspnea, or sudden unexplained clinical deterioration. D-dimer levels within 24 hours (h) from CTPA were obtained. In addition, all the components relevant for Wells score and PESI scale systems were noted (8-10). All patients enrolled in the study were over the age of 18. They were managed in accordance with the COVID-19 treatment protocol of the Turkish Health Ministry, and weight-based thromboprophylaxis was started with low-molecular-weight heparin (LMWH), enoxaparin sodium once daily for all inpatients with COVID-19 pneumonia if no contraindication (12). Nonetheless, it was observed that the course of treatment was continued for patients who were already on non-vitamin K antagonist oral anticoagulant (NOAC) or vitamin K antagonist (VKA).

The clinical findings of the hospitalized patients were classified as moderate or severe according to the NIH criteria (13). CT graded the severity of COVID-19 pneumonia lung paraenchymal changes into three categories; low, moderate, and severe involvement (14). CTPA images were evaluated for the presence of PE, anatomic distribution of PE such as major vessel or minor vessel involvement. Cases were categorized as patients with PE and patients with non-PE on the basis of CTPA imaging. PE related to major vessel was defined as main pulmonary artery and/or lobar artery involvement, while minor vessel was defined as segmental artery and/or subsegmental involvement. Early PE diagnosis was discretionary when diagnosis was confirmed within 24 h of admission. The Wells score and PESI scale systems were calculated by the authors. The primary outcome was PE confirmed by CTPA. It was also assessed the death, admission to the ICU, hospital length of stay, D-dimer value, Wells score, and PESI scale in COVID-19 pneumonia with PE.

The research protocol was approved by the Ethics Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2022-02-11, date: 17.01.2022) and was conducted following the principles of the Declaration of Helsinki. The requirement for informed consent from individual patients was waived because of the observational retrospective design of this study.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) v. 26. Continuous data were reported as the mean ± standard deviation for normally distributed data or the median and interquartile range (IQR) for non-normally distributed data. Categorical data are reported as counts and percentages. Numerical variables are given as frequencies (percentages). Student's t-test was used for two-group comparisons of quantitative data with normal distribution, and the Mann-Whitney U test was used for two-group comparisons of data that did not show normal distribution. For comparison of qualitative data, Pearson's chi-square test, Fisher's Exact test were used. Diagnostic screening tests [sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)] and receiver operating characteristic (ROC) curve analysis were performed and area under the curve (AUC) calculated to identify the cutoff value for the D-dimer level. Multivariate logistic regression analysis was performed to identify risk factors for developing PE. Significance was assessed at least at $p<0.05$ level.

RESULTS

All consecutive patients who underwent CTPA scanning for PE were excluded. Ultimately, 220 patients met all the inclusion criteria. Of these, 96 (43.63) patients had PE. Flow chart of the study population in Figure 1. The mean age was 65.7±16.28 (range 24-94 years), and the male to female ratio was 51.4:48.6. Dyspnea (184-83.6%), cough (48-21.8%), and

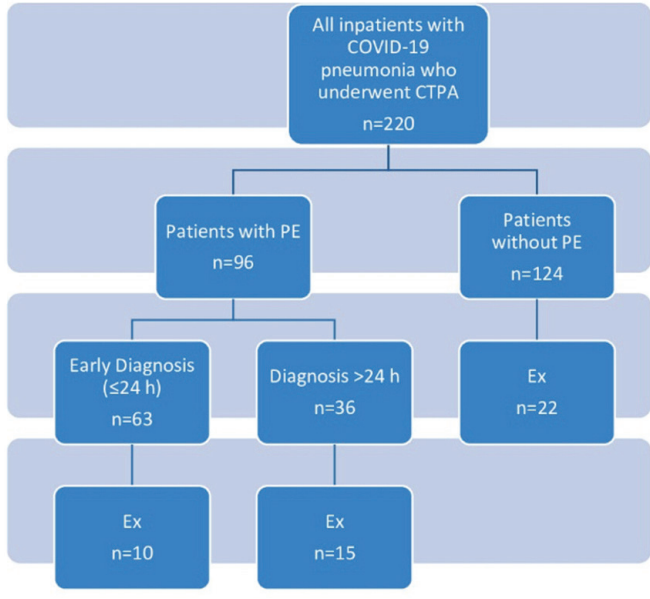

Figure 1. Flow chart of the study population
CTPA: Computed tomography pulmonary angiography, PE: Pulmonary embolism, COVID-19: Coronavirus disease-2019

Table 1. Demographic and baseline clinical characteristics of study participants with and without pulmonary embolism

		All patients (n=220)	Pulmonary embolism		
			Absent (n=124)	Present (n=96)	p-value
Age, years mean ± SD		65.70±16.28	66.94±15.17	64.10±17.56	[a]0.210
Sex, n (%)	Male	113 (51.4)	71 (57.3)	42 (43.8)	[b]0.047*
	Female	107 (48.6)	53 (42.7)	54 (56.3)	
Symptoms, n (%)	Dyspnea	184 (83.6)	106 (85.5)	78 (81.3)	[b]0.400
	Cough	48 (21.8)	30 (24.2)	18 (18.8)	[b]0.332
	Chest pain	32 (14.5)	11 (8.9)	21 (21.9)	[b]0.007**
	Haemoptysis	11 (5.0)	3 (2.4)	8 (8.3)	[c]0.062
	Nausea	3 (1.4)	1 (0.8)	2 (2.1)	[c]0.582
	Fever	17 (7.7)	9 (7.3)	8 (8.3)	[b]0.767
	Weakness	29 (13.2)	12 (9.7)	17 (17.7)	[b]0.081
	Back pain	3 (1.4)	1 (0.8)	2 (2.1)	[c]0.582
	Abdominal pain	10 (4.5)	5 (4.0)	5 (5.2)	[c]0.751
	Leg swelling or pain	4 (1.8)	0 (0.0)	4 (4.2)	[c]0.035*
	Dizziness	8 (3.6)	5 (4.0)	3 (3.1)	[c]1.000
	Syncope	4 (1.8)	3 (2.4)	1 (1.0)	[c]0.634
Time between symptom onset and hospitalization, days mean ± SD		7.25±5.03	6.77±5.43	7.86±4.41	[d]0.006**
Time between symptom onset to CTPA, days mean ± SD		9.45±6.72	8.74±7.13	10.36±6.06	[d]0.005**
Time between admission and CTPA, days mean ± SD		3.13±4.52	2.74±4.13	3.64±4.96	[d]0.057
Early PE diagnosis (≤24 h from admission), n (%)				63 (65.62)	
Physical findings, mean ± SD					
Body temperature, °C		36.76±0.5	36.74±0.52	36.79±0.48	[d]0.134
Systolic blood pressure, mmHg		125.79±15.73	124.27±14.67	127.75±16.87	[d]0.073
Diastolic blood pressure, mmHg		68.2±8.96	67.93±8.53	68.55±9.53	[d]0.149
Heart rate per minute		89.29±13.12	87.72±13.83	91.32±11.92	[a]0.043*
Respiratory rate, breaths per minute		25.32±5.26	23.16±4.11	28.11±5.29	[d]0.001**
SpO_2 under oxygen support		93.72±6.29	94.32±2.01	92.94±9.22	[d]0.043*
Oxygen support, L/per min		8.07±7.37	7.48±6.85	8.82±7.97	[d]0.262
Comorbidities, n (%)		183 (83.2)	109 (87.9)	74 (77.1)	[b]0.033*
Hypertension		122 (55.5)	74 (59.7)	48 (50.0)	[b]0.152
Diabetes mellitus		81 (36.8)	51 (41.1)	30 (31.3)	[b]0.132
Coronary artery disease		53 (24.1)	32 (25.8)	21 (21.9)	[b]0.499
Atrial fibrillation		16 (7.3)	11 (8.9)	5 (5.2)	[b]0.300
Congestive heart failure		39 (17.7)	23 (18.5)	16 (16.7)	[b]0.717
Dyslipidemia		21 (9.5)	14 (11.3)	7 (7.3)	[b]0.317

Table 1. Continued

Cerebrovascular disease		16 (7.3)	10 (8.1)	6 (6.3)	[b]0.607
Chronic kidney disease		26 (11.8)	16 (12.9)	10 (10.4)	[b]0.571
Rheumatic disease		7 (3.2)	4 (3.2)	3 (3.1)	[c]1.000
Malignancy		30 (13.6)	21 (16.9)	9 (9.4)	[b]0.105
Valvular heart disease		8 (3.6)	5 (4.0)	3 (3.1)	[c]1.000
Peripheral artery disease		7 (3.2)	6 (4.8)	1 (1.0)	[c]0.140
COPD		22 (10.0)	13 (10.5)	9 (9.4)	[b]0.786
Asthma		18 (8.2)	10 (8.1)	8 (8.3)	[b]0.942
Disease severity status, n (%)	Severe	182 (82.7)	103 (83.1)	79 (82.3)	[b]0.880
	Moderate	38 (17.3)	21 (16.9)	17 (17.7)	
Hospital length of stay, days mean ± SD		18.50±14.58	18.81±16.88	18.09±10.99	[d]0.350
ICU length of stay, days mean ± SD		3.77±7.76	3.38±7.47	4.28±8.14	[d]0.377
Outcomes, n (%)					
Admission to ICU, n (%)		71 (32.3)	38 (30.6)	33 (34.4)	[b]0.557
Death in the ICU, n (%)		43 (19.5)	20 (16.1)	23 (24.0)	[b]0.146
Death, n (%)		47 (21.4)	22 (17.7)	25 (26.0)	[b]0.136

COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, PE: Pulmonary embolism, CTPA: Computed tomography pulmonary angiography, ICU: Intensive care unit
[a]Student's t-test; [b]Pearson chi-square test; [c]Fisher's Exact test; [d]Mann-Whitney U test *p<0.05; **p<0.01. Bold indicates statistical significance. Categorical data are presented as n (%). Continuous data are presented as mean ± SD

chest pain (32-14.5%) were the most common symptoms. Time between symptom onset and hospitalization was 7.25±5.03 days (IQR 6 range 4-10) was. The mean length of hospital stay was calculated as 18.50±14.58 days. Seventy-one (32.3%) cases were referred to the ICU. Forty-seven cases (21.4%) died, 43 (19.5%) of whom were in the ICU. The incidence of PE diagnosis was 43.63% (96/220) in patients who underwent CTPA with suspicion of PE. In addition, 65.62% (63/96) of all PE cases were diagnosed with PE within the first 24 h after admission. Table 1 summarizes the baseline characteristics of the study population.

The incidence of PE was statistically significantly higher in women than in men (p<0.05). The mean age of women in the PE group was higher than men (p=0.008; p<0.01) (Summary statistics by age and gender in Supplementary Table S3). The incidence of chest pain and lower leg pain in patients with PE was found to be statistically significantly higher than that in patients without PE (respectively, p<0.01 vs. p<0.05). Time between symptom onset and hospitalization in patients with PE was found to be significantly higher than that in patients without PE (7.86±4.41 vs. 6.77±5.43 days; p<0.01). Time between symptom onset to CTPA in cases with PE was significantly higher than that in cases without PE (10.36±6.06 vs. 8.74±7.13 days; p<0.01).

The D-dimer value of the cases with PE was found to be significantly higher than that of the cases without embolism (4.5±2.68 vs. 3.71±3.6; p<0.01) (Table 2). The D-dimer/hs-TnT ratio was significantly higher in the PE group (153.91±323.51 vs. 55.40±156.75; p<0.01). Figure 2 evaluates the performance of the D-dimer assay in determining PE as a ROC curve. AUC of the ROC curve is 0.626 (95% CI = 0.550-0.703; p=0.001). A D-dimer with a best cut-off value of 3.95 µg FEU/mL provided a sensitivity of 64.21%, specificity of 69.11%, PPV of 61.6%, NPV of 71.4%, and odds ratio (OR) of 4.013 (95% CI: 2.275-7.080).

PE anatomic localization distribution was as follows: 56.25% (54 cases) unilateral, 62.5% (60 cases) multiple, 40.6% (39 cases) multilobar/bilateral, 86.5% (83) right-sided, and 66.6% (64 cases) lower lobe artery. 31.25% (30 cases) major vessels (main pulmonary artery and lobar pulmonary artery) and 34.37% (33 cases) minor vessels (segmental and subsegmental artery) localized PEs were detected. Severe CT lung paraenchymal involvement was significantly higher in PE cases (p<0.05) (Table 3).

Classifying all cases according to the Wells three-level score, 215 (97.7%) cases had intermediate clinical risk and 5 (2.3%) cases had high clinical risk (Table 4). The Wells

Table 2. Laboratory data of the study population COVID-19 patients at the time of CTPA

Laboratory findings Mean ± SD	Pulmonary embolism			
	All patients (n=220)	Absent (n=124)	Present (n=96)	p-values
Neutrophil count, cells/mL	8.87±4.78	8.63±4.37	9.19±5.26	[d]0.748
Lymphocytes count, cells/mL	1.32±1.2	1.41±1.43	1.2±0.82	[d]0.392
Neutrophil/lymphocyte ratio	11.81±14.79	11.46±16.27	12.27±12.73	[d]0.306
Platelet count, $10^3/mm^3$	241.73±121.15	232.09±120.77	254.07±121.15	[a]0.183
Hematocrit, %	35.18±6.65	35.24±7.07	35.1±6.1	[a]0.878
Glucose, mg/dL	163.52±70.48	164.12±74.61	162.76±65.18	[d]0.746
Urea, mg/dL	54.19±43.76	57.14±44.93	50.4±42.15	[d]0.109
Creatinine, mg/dL	1.3±2.08	1.32±1.82	1.29±2.4	[d]0.103
ALT, U/L	38.54±66.25	36.38±70.78	41.33±60.16	[d]0.101
AST, U/L	45.63±70.50	47.30±86.39	43.47±42.26	[d]0.099
Albumin, g/dL	33±6.13	32.81±6.36	33.26±5.86	[a]0.599
LDH, U/L	449.42±498.49	438.73±484.11	463.23±518.71	[d]0.127
C-reactive protein, mg/L	124.82±89.74	125.26±95.88	124.24±81.6	[d]0.733
Procalcitonin, ng/mL	1.22±4.11	1.16±3.45	1.3±4.85	[d]0.125
Ferritin, µg/L	964.59±1457.21	967.11±1487.59	961.33±1424.76	[d]0.390
D-dimer, µg FEU/mL	4.06±3.25	3.71±3.6	4.5±2.68	**[d]0.001****
D-dimer >1 µg FEU/mL n, (%)				
No	26 (11.8)	15 (12)	11 (11.4)	b0.841
Yes	194 (88.2)	109 (88)	85 (88.6)	
Troponin T is highly sensitive, ng/mL	26.16±51.53	27.87±46.56	23.89±57.64	**[d]0.002****
D-dimer/troponin T high sensitive	97.75±247.11	55.40±156.75	153.91±323.51	**[d]0.001****
Fibrinogen, mg/dL	618.68±203.47	622.87±220.64	613.23±179.76	[a]0.724
International normalized ratio	1.24±0.48	1.20±0.44	1.28±0.53	[d]0.183
ProBNP, ng/L	4614.91±6291.9	3442.77±3507.28	5179.27±7258.57	[d]0.851

SD: Standard deviation, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CTPA: Computed tomography pulmonary angiography, COVID-19: Coronavirus disease-2019
[a]Student's t-test, [b]Pearson chi-square test, [c]Fisher's exact test, [d]Mann-Whitney U test, *p<0.05, **p<0.01. Categorical data are presented as n (%). Continuous data are presented as mean ± SD. Bold indicates statistical significance

three-level score was similar in the groups with and without PE groups (p>0.05). If the study population was classified according to the Wells two-level score, the Wells score of >4 (PE likely) was 9/124 (7.3%) without PE vs. 16/96 (16.7%) with PE (p<0.05). When the Wells score and D-dimer values were evaluated together, D-dimer value of the cases with PE in the PE unlikely probability group was found to be statistically significantly higher than the cases without PE (p<0.01) (Figure 3) (Likely considered as Wells score of >4). Considering the Wells score components in patients with PE, signs or symptoms of DVT (4-4.2%; p<0.05), previous DVT or PE (6-6.3%; p<0.01), and immobilization/surgery in the past 4 weeks (14-14.6%; p<0.05) were found to be significantly higher compared with patients without PE. The mean PESI scale was 120.35±49.36 (median 32-223) (Table 4). It was observed that 39.6% (n=38) of the cases were PESI Class V (PESI scale distribution and mortality rates in Supplementary Table S4).

Female sex, leg swelling or pain, heart rate, respiratory rate, lower SpO_2 levels, late hospitalization after symptom onset, time between symptom onset to CTPA, D-dimer, D-dimer/hs-TnT, higher chest CT involvement score, signs or symptoms of DVT, previous thromboembolic disease, and immobilization/surgery in the past 4 weeks were all significantly associated with PE by univariate analysis. When the variables found to be effective on PE (p<0.200) were put on backward stepwise multivariate logistic regression

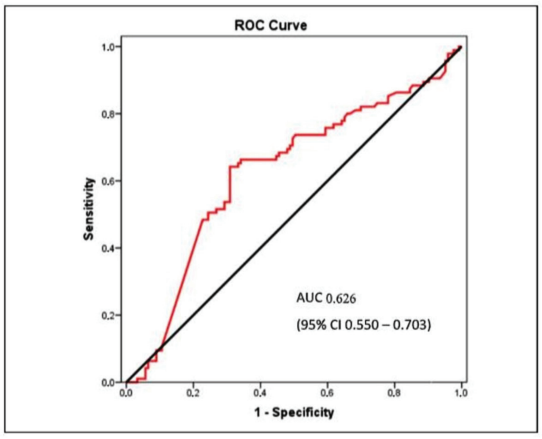

Figure 2. Receiver operating characteristic curve for D-dimer for the diagnosis of pulmonary embolism
AUC: Area under the curve, ROC: Receiver operating characteristic, CI: Confidence interval

Table 3. Findings on CTPA in the study population

	All patients (n=220)	Non-PE (n=124)	PE (n=96)	p-values
CT involvement, n (%)				[b]0.040*
Low	47 (21.4)	25 (20.2)	22 (22.9)	
Moderate	96 (43.6)	63 (50.8)	33 (34.4)	
Severe	77 (35.0)	36 (29.0)	41 (42.7)	
Major vessel			30 (31.2)	
Only the main pulmonary artery			13 (13.5)	
Only the lobar pulmonary artery			17 (18.8)	
Minor vessel			33 (34.3)	
Only segmental artery			23 (23.9)	
Only the subsegmental artery			10 (10.4)	
Both (major + minor)			33 (34.3)	
Lower lobe artery			64 (66.6)	
Bilaterally			42 (43.75)	
Unilaterally			54 (56.25)	
Right sided			83 (86.45)	
Multiple			54 (56.3)	
Multilobar/ bilaterally			39 (40.6)	

Values are n (%). [b]Pearson chi-square test
PE: Pulmonary embolism, CT: Computed tomography, CTPA: Computed tomography pulmonary angiography

analysis, the model was found to be significant and had a coefficient of determination 76.8%. Because of the logistic regression analysis, female gender, hemoptysis, time between symptom onset and hospitalization, time between symptom onset and CTPA, time between admission and CTPA, systolic blood pressure, and respiratory rate were independent risk factors for PE (Table 5). The presence of female sex and haemoptysis both showed a higher risk of acquiring PE by 2.643 (OR 2.643, 95% CI: 1.291-5.414, $p<0.05$), and 10.6 (OR 10.698, 95% CI: 1.886-60.68, $p<0.05$), respectively, by backward logistic regression analysis (Table 5).

Patients were also evaluated about drugs that were regularly taken before hospitalization and continued during hospitalization. Only VKA use in the PE group was found to be statistically significantly higher ($p<0.05$). Three of seven patients were using VKA for AF diagnosis before hospital admission and PE had developed despite anticoagulant therapy. However, the remaining 4 patients began VKA treatment after the diagnosis of PE. The LMWH title covered both prophylaxis and PE treatment (Table 6).

Although not statistically significant, the mortality was higher in individuals with PE than in those with both deaths in the ICU (24% vs. 16.1%) and overall mortality (26% vs. 17.7%) ($p>0.05$).

DISCUSSION

This research provides information about the incidence of PE in patients hospitalized for COVID-19 pneumonia at the COVID-19 departments of our hospital. We found 96 (43.63%) patients with verified PE and COVID-19 pneumonia out of 220 CTPAs performed. These data strengthen the hypothesis that COVID-19 patients have an increased thromboembolic risk. Females with hemoptysis

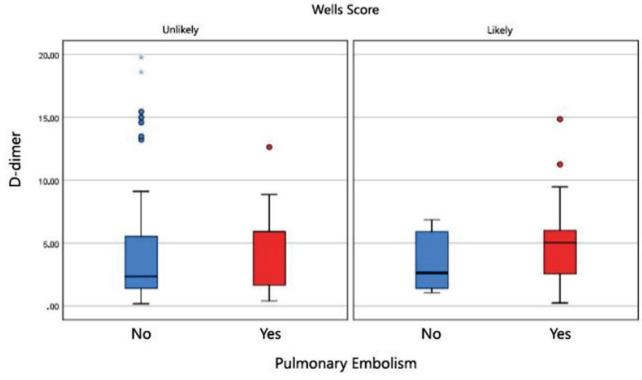

Figure 3. Distribution of D-dimer values in patients at likely and unlikely probability for pulmonary embolism (Wells score of >4, PE likely)

have a higher risk of PE occurrence. Patients with PE who have severe lung paraenchymal involvement are more common on CT. D-dimer levels are higher among COVID-19 hospitalized patients with PE, but its use to exclude PE in this population may have limited clinical utility. Although a Wells score of 4 or more points helps to predict PE in our cohort, the outcome can be present even with lower scores. The PESI scale in patients with PE secondary to COVID-19 underrates the risk of in-hospital mortality.

Our cohort showed a diagnostic performance of 43.63% in hospitalized patients with SARS-CoV-2 who underwent CTPA because of a clinical suspicion for PE. In previous

Table 4. Predictive scores of study participants

	All patients (n=220)	Pulmonary embolism		p-value
		Absent (n=124)	Present (n=96)	
Components of Wells score, n (%)				
Signs or symptoms of DVT	4 (1.8)	0 (0.0)	4 (4.2)	[c]**0.035***
Heart rate >100/min	38 (17.3)	18 (14.5)	20 (20.8)	[b]0.219
Previous thromboembolic disease	6 (2.7)	0 (0.0)	6 (6.3)	[c]**0.006****
Immobilisation/surgery in the past 4 weeks	22 (10.0)	8 (6.5)	14 (14.6)	[b]**0.048***
Haemoptysis	11 (5.0)	3 (2.4)	8 (8.3)	[c]0.062
Malignancy	30 (13.6)	21 (16.9)	9 (9.4)	[b]0.105
Wells score				[c]0.655
Low risk (0-1 points)	0	0	0	
Intermediate risk (2-6 points)	215 (97.7)	122 (98.4)	93 (96.9)	
High risk (>6 points)	5 (2.3)	2 (1.6)	3 (3.1)	
Likely >4	25 (11.4)	9 (7.3)	16 (16.7)	[b]**0.029**
Unlikely ≤4	195 (88.6)	115 (92.7)	80 (83.3)	
PESI score			120.35±49.36	
Class I			10 (10.4)	
Class II			15 (15.6)	
Class III			23 (24.0)	
Class IV			10 (10.4)	
Class V			38 (39.6)	

[b]Pearson chi-square test, [c]Fisher's Exact test, *p<0.05, **p<0.01. Categorical data are presented as n (%). Continuous data are presented as mean ± standard deviation.
Bold indicates statistical significance
DVT: Deep vein thrombosis, PESI: Pulmonary embolism severity index

Table 5. Multivariate logistic regression analysis of risk factors for PE

	OR	p-value	95% CI	
			Lower	Upper
Female sex	2.643	**0.008****	1.291	5.414
Haemoptysis	10.698	**0.007****	1.886	60.681
Time between symptom onset and hospitalization, days	2.407	**0.029***	1.094	5.297
Time between symptom onset to CTPA, days	0.431	**0.036***	0.196	0.945
Time between hospitalization and CTPA, days	2.432	**0.038***	1.049	5.639
Systolic blood pressure, mmHg	1.037	**0.002****	1.013	1.062
Respiratory rate, breaths per minute	1.357	**0.001****	1.231	1.495

OR: Odds ratio, CI: Confidence interval, CTPA: Computed tomography pulmonary angiography, PE: Pulmonary embolism

Table 6. Medication during hospitalization before and after PE diagnosis

		All patients (n=220)	Pulmonary embolism		
			Absent (n=124)	Present (n=96)	
		n (%)	n (%)	n (%)	p-value
Drugs used during hospitalization	ASA	39 (17.7)	24 (19.4)	15 (15.6)	[b]0.473
	Clopidogrel	20 (9.1)	13 (10.5)	7 (7.3)	[b]0.414
	DAPT	13 (5.9)	9 (7.3)	4 (4.2)	[b]0.335
	VKA	8 (3.6)	1 (0.8)	7 (7.3)	[c]**0.023***
	NOAC	7 (3.2)	5 (4.0)	2 (2.1)	[c]0.473
	β-Blocker	51 (23.2)	31 (25.0)	20 (20.8)	[b]0.468
	Ca++ channel blocker	25 (20.2)	25 (26.0)	50 (22.7)	[b]0.302
	ACE-I	20 (9.1)	11 (8.9)	9 (9.4)	[b]0.897
	ARB	21 (9.5)	14 (11.3)	7 (7.3)	[b]0.317
	Statin	21 (9.5)	14 (11.3)	7 (7.3)	[b]0.317
	LMWH	201 (91.4)	114 (91.9)	87 (90.6)	[b]0.731
Trombolytic therapy	Alteplase	7 (3.2)		7 (7.3)	-

PE: Pulmonary embolism, ASA: Acetylsalicylic acid, DAPT: Dual antiplatelet therapy, VKA: Vitamin K antagonist, NOAC: Non-vitamin K antagonist oral anticoagulant drugs, ACE-I: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, LMWH: Low molecular weight heparin
Alteplase, recombinant human tissue-type plasminogen activator (t-PA). Categorical data are presented as n (%). [b]Pearson chi-square test. [c]Fisher's Exact test. *p<0.05. Bold indicates statistical significance.

studies, the incidence of PE in COVID-19 cases was reported to be 14-38% (3,15-18). In the studies conducted with patients who were hospitalized for any reason in the pre-COVID-19 period, the diagnosis of PE with CTPA was found to be 12-17% (19). Various studies have reported different values for PE incidence because of diverse protocols or the availability of CTPA (3,15,17,18). The incidence of PE was higher in prospective studies, in studies that did not include anticoagulation therapy, in ICU admission or critical cases, and in studies in which CTPA was applied to all cases according to a meta-analysis (1).

Unlike previous studies, the female gender had a 2.6 times higher risk of developing PE in our study. PE cases were elderly female cases consistent with the general population (20). Although many studies on COVID-19 announced that the frequency of PE, severe disease, and mortality were higher in males, some studies reported that there was no difference in terms of gender (5,21).

The incidence of hemoptysis was calculated as 8.3% (8 cases) in the PE group in our study. The incidence of hemoptysis was 2.2% in a study of PE developing in cases with COVID-19; PE in non-COVID cases in the general population has been reported as 13% (Table 5) (22,23).

The D-dimer level was significantly higher in COVID-19 pneumonia patients with PE than in those without PE, consistent with previous data (5,7). Meanwhile, high D-dimer levels were common in COVID-19 patients even in the absence of PE in our study, in concordance with previous studies (7,24). Ultimately, higher D-dimer levels are not only a marker of pneumonia severity but also linked with a higher risk of PE (21,25,26). A higher cut-off value specifically as 3.95 µg FEU/mL for D-dimer, could predict the risk of PE in COVID-19 patients with a sensitivity of 64.21% and specificity 69.11%. AUROC was 0.626 in our calculations, which demonstrates the lower discriminative power of D-dimer levels used to detect PE in previous research (1,24,25,27). There are many studies reporting different sensitivity and specificity with different threshold values (15,17,18,24,28,29). Indeed, higher cut-off values than those conventionally used (1000 mg/L) reduced the sensitivity of D-dimer levels as a scanning examination to rule out PE (1). Therefore, some studies recommend D-dimer thresholds used in outpatients who have no COVID-19 to safely exclude PE (27,29). Elevation of D-dimer levels in the COVID-19 population may originate in the presence of various conditions such as prothrombotic coagulopathy or pulmonary microvascular thrombosis, and systemic inflammation (6,7).

There was a significant association between the D-dimer/hs-TnT ratio in PE. Cardiac troponins may be elevated in patients with right ventricular dysfunction or severe PE, and high troponin levels are associated with poor prognosis (27,30). One study reported that the D-dimer/troponin I

ratio is a simple and useful test to distinguish between PE and acute non-ST-segment elevation myocardial infarction (31). Studies on COVID-19 have reported that high troponin and ProBNP levels are associated with poor prognosis and mortality (32). Ultimately, natriuretic peptides and troponins can increase in various pathological situations and are not specific to VTE. Simultaneously, both BNP and troponin levels can be used to assess the risk of intermediate short-term adverse events in patients with PE (27). In patients with acute dyspnea and high PE clinical suspicion, high troponin values are also expected. While higher troponin levels in the non-PE group indicate cardiac dysfunction, its lower rate in the PE group can be interpreted as an appropriate cohort of the studied patient group, since this finding indicates that acute dyspnea is non-cardiac in the PE clinic. The fact that ProBNP levels are not different in the presence of PE or cardiac dyspnea in patients presenting with acute dyspnea may support this hypothesis.

Only 16.7% of patients with PE had a Wells score of 4 points or higher, and 3.1% of patients with PE had a high risk probability (>6 points). In the Wells score high-risk probability group, only 3 out of 5 cases were PE; however, PE was detected in 215 cases in the intermediate-probability risk group, and these results showed that the incidence of PE was higher than expected in the intermediate group.

These findings indicate that the Wells score may be insufficient or unreliable in predicting PE. Although some studies have previously shown that a Wells score of 4 or more points can predict PE in patients with COVID-19, there are also contradicting studies reporting that the Wells score is a weak indicator for predicting PE in patients with COVID-19 (5,15,17,29,33,34). Nonetheless, there are also studies reporting that combining Wells score and D-dimer levels is a more logical approach in predicting PE in COVID-19 cases (25,34,35).

If Wells score components were evaluated separately, the presence of symptoms or signs of DVT, history of thromboembolic disease, and immobilization/surgery (in the past 4 weeks) were significantly higher in patients with PE, although in small numbers. At the same time, it was reported that regarding traditional risk factors (advanced age, history of venous thromboembolic disease, thrombophilia, cancer, smoking, diabetes, hypertension, chronic heart failure, or coronary artery disease) for VTE, there were no differences between patients with and without PE (5,21). However, one study reported that DVT signs and symptoms were associated with PE (15). In our study, lower extremity Doppler ultrasonography (USG) was performed in only 4 patients. Higher rates of DVT have been reported in studies that screened all patients with Doppler USG, regardless of symptoms (36). The Wells score is based on the assumption that PE is a consequence of DVT or immobilization; however, it has been reported that 55-85% of COVID-19-related PE cases do not have DVT (1,33). PE may arise from direct endothelial cell damage caused by the virus or from an inflammatory process related to alveolar damage in COVID-19 patients (4-6). This may be the reason why the Wells score performs weakly in predicting COVID-19-related PE. Although the pathophysiology of PE development in COVID-19 has aspects that can be explained by the Virchow triad; COVID19-associated hypercoagulability is still special and distinctive with involvement of the immune system (4).

Our results showed that the PESI scale underestimates the risk of inhospital mortality, similar to other studies; however, it maintains its acceptable ability to discriminate patients with Class I and Class V (11,27). Ultimately, according to our findings, the Wells score was found insufficient to predict the diagnosis of PE, and the PESI scale was again inadequate to determine the prognosis of PE.

The same as earlier research, although there was no significant difference in mortality between the PE group and the non-PE group, the mortality was non-significantly higher in the PE group (26%, 25 cases) (5,22). Contradicting with this fact, there are studies reporting that mortality is high in cases of PE with COVID-19, as well as studies mentioning increased mortality compared to non-COVID cases (22,28).

Consistent with published studies, in our cohort, there was a significant association between PE and severity of COVID-19 disease paraenchymal involvement on CTPA imaging (17,37). In our study, major vessel and minor vessel involvement rates were found to be very close to each other (30 cases, 31.25% vs. 33 cases, 34.37%). There are also contradicting studies in which peripheral and lower lobe artery involvement are reported to be higher (15,17,22) and studies reporting that 44-56% central/lobar pulmonary artery involvement is more frequent (38).

In our cohort, the presence of clinical signs of DVT in COVID-19 patients with PE was very small in number; also, similar rates of major and minor vessel involvement of PE suggest that both conventional thromboembolic origin and *in situ* immunothrombosis may be involved in the pathophysiology of COVID-19-associated PE (5,6).

The duration between the onset of symptoms and admission to the hospital and time to CTPA were longer in the PE group. The reasons for these findings may be longer bed rest and/or immobilization; late initiation of prophylactic anticoagulants, or an unknown immune system-related pathophysiological mechanism (28). Haemoptysis, chest pain, lower leg pain,

and dyspnea symptoms should be noted.

This study showed that 65.62% of all PE cases were diagnosed with CTPA within the first 24 h of admission. In various studies, early diagnosis rates ranged from 14.2% to 68.8% (11,16). Studies have shown that the diagnosis of PE is made earlier with increased CTPA requests in the pre-ICU stage after the first wave in cases with COVID-19, and as a result, the risk of PE in the ICU is reduced (37). The diagnosis of most cases with PE within the first 24 h in the early stage of this process suggests that hypercoagulation may have started before hospitalization (15,28).

The presence of MicroCLOTS and macrovascular disease findings in PE developing in COVID-19 cases indicates that there are still many things unknown; it also highlights the difficulty of distinguishing between clinical and/or CTPA findings and separating conventional thromboembolism and *in situ* immunothrombosis (5,6).

The limitations of this study include its retrospective nature and small sample size. There is a potential selection bias because only cases with clinical and laboratory findings and suspected PE are evaluated with CTPA. Doppler ultrasound imaging of the lower extremity for deep venous thrombosis and transthoracic echocardiography could not be performed.

CONCLUSION

Our research showed that PE appears to be a common complication of SARS-CoV-2 infection, the Wells score used in the general population was not helpful in the diagnosis of PE, and the PESI score was unreliable in predicting the mortality risk of PE in these patients. Higher D-dimer values may detect COVID-19-related PE. These findings indicate that CT with contrast could be more widely used when assessing individuals with COVID-19 pneumonia, particularly in those with elevation of D-dimer and presence of hemoptysis.

ETHICS

Ethics Committee Approval: The research protocol was approved by the Ethics Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2022-02-11, date: 17.01.2022) and was conducted following the principles of the Declaration of Helsinki.

Informed Consent: The requirement for informed consent from individual patients was waived because of the observational retrospective design of this study.

Authorship Contributions

Surgical and Medical Practices: I.K.A., M.B., Concept: I.K.A., M.B., Design: I.K.A., M.B., Data Collection or Processing: I.K.A., M.B., Analysis or Interpretation: I.K.A., M.B., Literature Search: I.K.A., M.B., Writing: I.K.A., M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Suh YJ, Hong H, Ohana M, Bompard F, Revel MP, Valle C, et al. Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. Radiology 2021;298:E70-80.
2. Boyd S, Sheng Loh K, Lynch J, Alrashed D, Muzzammil S, Marsh H, et al. The Incidence of Venous Thromboembolism in Critically Ill Patients with SARS-CoV-2 Infection Compared with Critically Ill Influenza and Community-Acquired Pneumonia Patients: A Retrospective Chart Review. Med Sci (Basel) 2022;10:30.
3. Bompard F, Monnier H, Saab I, Tordjman M, Abdoul H, Fournier L, et al. Pulmonary embolism in patients with COVID-19 pneumonia. Eur Respir J 2020;56:2001365.
4. Mehta JL, Calcaterra G, Bassareo PP. COVID-19, thromboembolic risk, and Virchow's triad: Lesson from the past. Clin Cardiol 2020;43:1362-7.
5. Mestre-Gómez B, Lorente-Ramos RM, Rogado J, Franco-Moreno A, Obispo B, Salazar-Chiriboga D, et al. Incidence of pulmonary embolism in non-critically ill COVID-19 patients. Predicting factors for a challenging diagnosis. J Thromb Thrombolysis 2021;51:40-6.
6. Ciceri F, Beretta L, Scandroglio AM, Colombo S, Landoni G, Ruggeri A, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc 2020;22:95-7.
7. Zhan H, Chen H, Liu C, Cheng L, Yan S, Li H, et al. Diagnostic Value of D-Dimer in COVID-19: A Meta-Analysis and Meta-Regression. Clin Appl Thromb Hemost 2021;27:10760296211010976.
8. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med 2001;135:98-107.
9. Wolf SJ, McCubbin TR, Feldhaus KM, Faragher JP, Adcock DM. Prospective validation of Wells Criteria in the evaluation of patients with suspected pulmonary embolism. Ann Emerg Med 2004;44:503-10.
10. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172:1041-6.
11. Muñoz OM, Ruiz-Talero P, Hernández-Florez C, Lombo-Moreno CE, Casallas-Rivera MA, Mayorga-Hernández CA. Validation of the PESI Scale to Predict in-Hospital Mortality in Patients with Pulmonary Thromboembolism Secondary to SARS CoV-2 Infection. Clin Appl Thromb Hemost 2022;28:10760296221102940.
12. Republic of Turkey Ministry of Health. COVID-19 (SARS-CoV-2 Infection) Guide. https://covid19.saglik.gov.tr/TR-66926/eriskin-hasta-tedavisi.html
13. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. http://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum
14. Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, et al. Chest CT Severity Score: An Imaging Tool for Assessing Severe COVID-19. Radiol Cardiothorac Imaging 2020;2:e200047.
15. Whyte MB, Kelly PA, Gonzalez E, Arya R, Roberts LN. Pulmonary embolism in hospitalised patients with COVID-19. Thromb Res 2020;195:95-9.

16. Jevnikar M, Sanchez O, Chocron R, Andronikof M, Raphael M, Meyrignac O, et al. Prevalence of pulmonary embolism in patients with COVID-19 at the time of hospital admission. Eur Respir J 2021;58:2100116.
17. Ooi MWX, Rajai A, Patel R, Gerova N, Godhamgaonkar V, Liong SY. Pulmonary thromboembolic disease in COVID-19 patients on CT pulmonary angiography - Prevalence, pattern of disease and relationship to D-dimer. Eur J Radiol 2020;132:109336.
18. Ventura-Díaz S, Quintana-Pérez JV, Gil-Boronat A, Herrero-Huertas M, Gorospe-Sarasúa L, Montilla J, et al. A higher D-dimer threshold for predicting pulmonary embolism in patients with COVID-19: a retrospective study. Emerg Radiol 2020;27:679-89.
19. Chen Z, Deblois S, Toporowicz K, Boldeanu I, Francoeur MO, Sadouni M, et al. Yield of CT pulmonary angiography in the diagnosis of acute pulmonary embolism: short report. BMC Res Notes 2019;12:41.
20. Tanabe Y, Yamamoto T, Murata T, Mabuchi K, Hara N, Mizuno A, et al. Gender Differences Among Patients With Acute Pulmonary Embolism. Am J Cardiol 2018;122:1079-84.
21. Fauvel C, Weizman O, Trimaille A, Mika D, Pommier T, Pace N, et al. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. Eur Heart J 2020;41:3058-68.
22. Miró Ò, Jiménez S, Mebazaa A, Freund Y, Burillo-Putze G, Martín A, et al. Pulmonary embolism in patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome. Eur Heart J 2021;42:3127-42.
23. Stein PD, Terrin ML, Hales CA, Palevsky HI, Saltzman HA, Thompson BT, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest 1991;100:598-603.
24. Vivan MA, Rigatti B, da Cunha SV, Frison GC, Antoniazzi LQ, de Oliveira PHK, et al R. Pulmonary embolism in patients with COVID-19 and D-dimer diagnostic value: A retrospective study. Braz J Infect Dis 2022;26:102702.
25. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020;18:1324-9.
26. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
27. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41:543-603.
28. Scudiero F, Silverio A, Di Maio M, Russo V, Citro R, Personeni D, et al. Pulmonary embolism in COVID-19 patients: prevalence, predictors and clinical outcome. Thromb Res 2021;198:34-9.
29. Silva BV, Jorge C, Plácido R, Mendonça C, Urbano ML, Rodrigues T, et al. Pulmonary embolism and COVID-19: A comparative analysis of different diagnostic models performance. Am J Emerg Med 2021;50:526-31.
30. Meyer T, Binder L, Hruska N, Luthe H, Buchwald AB. Cardiac troponin I elevation in acute pulmonary embolism is associated with right ventricular dysfunction. J Am Coll Cardiol 2000;36:1632-6.
31. Kim JY, Kim KH, Cho JY, Sim DS, Yoon HJ, Yoon NS, et al. D-dimer/troponin ratio in the differential diagnosis of acute pulmonary embolism from non-ST elevation myocardial infarction. Korean J Intern Med 2019;34:1263-71.
32. Caro-Codón J, Rey JR, Buño A, Iniesta AM, Rosillo SO, Castrejon-Castrejon S, et al. Characterization of NT-proBNP in a large cohort of COVID-19 patients. Eur J Heart Fail 2021;23:456-64.
33. Monfardini L, Morassi M, Botti P, Stellini R, Bettari L, Pezzotti S, et al. Pulmonary thromboembolism in hospitalised COVID-19 patients at moderate to high risk by Wells score: a report from Lombardy, Italy. Br J Radiol 2020;93:20200407.
34. Kirsch B, Aziz M, Kumar S, Burke M, Webster T, Immadi A, et al. Wells Score to Predict Pulmonary Embolism in Patients with Coronavirus Disease 2019. Am J Med 2021;134:688-90.
35. Raj K, Chandna S, Doukas SG, Watts A, Jyotheeswara Pillai K, Anandam A, et al. Combined Use of Wells Scores and D-dimer Levels for the Diagnosis of Deep Vein Thrombosis and Pulmonary Embolism in COVID-19: A Retrospective Cohort Study. Cureus 2021;13:e17687.
36. Artifoni M, Danic G, Gautier G, Gicquel P, Boutoille D, Raffi F, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. J Thromb Thrombolysis 2020;50:211-6.
37. Tsakok MT, Qamhawi Z, Lumley SF, Xie C, Matthews P, Gleeson F, et al. COVID-19 CT pulmonary angiogram examinations and reported pulmonary embolism incidence: comparison between peak first wave and early second wave. Clin Radiol 2021;76:310-2.
38. Léonard-Lorant I, Delabranche X, Séverac F, Helms J, Pauzet C, Collange O, et al. Acute Pulmonary Embolism in Patients with COVID-19 at CT Angiography and Relationship to d-Dimer Levels. Radiology 2020;296:E189-91.

Table S1. Wells clinical prediction rule for pulmonary embolism

Items	Clinical desicion rule points
Previous PE or DVT	1.5
Heart rate ≥100 bpm,	1.5
Immobilisation or surgery in the past 4 weeks	1.5
Haemoptysis	1
Active cancer	1
Clinical signs of DVT	3
Alterative diagnosis less likely than PE	3
Clinical probability	
Three-level score	
Low risk	0-1
Intermediate risk	2-6
High risk	≥7
Two-level score	
PE unlikely	0-4
PE likely	≥5

PE: Pulmonary embolism, bpm: Beats per minutes, DVT: Deep vein thrombosis

Table S2. Pulmonary embolism severity index in risk stratification

Parameter	Score
Age	Age in years
Male sex	+10 points
Cancer	+30 points
Chronic heart failure	+10 point
Chronic pulmonary disease	+10 point
Pulse rate ≥110 bpm,	+20 points
Systolic blood pressure <100 mmHg	+30 points
Respiratory rate >30 breaths per min	+20 points
Temperature <36 °C	+20 points
Altered mental status	+60 points
Arterial oxygen saturation <90%	+20 points
Risk strata	**Class I:** ≤65 points very low 30 day mortality risk (0-1.6%) **Class II:** 66-85 points low mortality risk (1.7-3.5%)
	Class III: 86-105 points moderate mortality risk (3.2-7.1%) **Class IV:** 106-125 points high mortality risk (4.0-11.4%) **Class V:** >125 points very high mortality risk (10.0-24.5%)

bpm: Beats per minutes

Table S3. Summary statistics by age and gender in study population

		Gender		
		Male	**Female**	**p-value**
Age mean ± SD	Non-PE	66.59±13.61	67.40±17.17	[a]0.771
	PE	58.81±18.09	68.22±16.13	[a]**0.008****

PE: Pulmonary embolism, SD: Standard deviation
[a]Student's t-test, **p<0.01

Table S4. PESI score distribution and mortality rates

PESI score	n (%)	Death	Predicting inpatient mortality	Predicting 30 day mortality
Class 1	10 (10.4)	0	0.8	0-1.6
Class 2	15 (15.6)	2 (2.8)	1.8	1.7-3.5
Class 3	23 (24.0)	5 (5.2)	4.2	3.2-7.1
Class 4	10 (10.4)	2 (2.8)	5.9	4.0-11.4
Class 5	38 (39.6)	16 (16.6)	15.8	10.0-24.5

PESI: Pulmonary embolism severity index