ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 4 | Volume: 19 | Year: 2023

MEDICAL JOURNAL OF BAKIRKÖY

www.bakirkoytip.org

ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 4 | 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: December 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

Index

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:352-359
DOI: 10.4274/BMJ.galenos.2023.2023.8-16

Research

Relation of NLR, PLR, LMR and RDW with Mortality and Type of Surgery

NLR, PLR, LMR ve RDW'nin Mortalite ve Cerrahi Tipi ile İlişkisi

Yusuf Özgüner, Savaş Altınsoy

Ankara Etlik City Hospital, Clinic of Anesthesiology and Reanimation, Ankara, Türkiye

ABSTRACT

Objective: Neutrophil, lymphocyte, monocyte, thrombocyte counts and as novel inflammatory factors, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and red cell distribution width (RDW) play an important role in the occurrence and development of diseases. In this study, it was aimed to investigate the relationship between preoperative NLR, PLR, LMR and RDW values of patients hospitalized in the intensive care unit (ICU) after oncological surgery, and the length of intensive care and mortality rates. In addition, it was aimed to compare the demographic, clinical characteristics and laboratory parameters of the patients between both groups.

Methods: Patients hospitalized in the ICU after oncological surgery were included in the study. The patients were divided into two groups as patients undergoing gastrointestinal malignancy (colorectal, stomach and hepatocellular) surgery (group 1) and patients who had undergoing urologic malignancy (kidney, bladder and prostate) surgery (group 2). Information regarding demographics (age and gender), comorbidities, neutrophil-lymphocyte-platelet counts, NLR-PLR-LMR-RDW values, length of ICU stay, acute physiology and chronic health evaluation II (APACHE-II) score, Glasgow coma scale and mortality rates were recorded.

Results: Two hundred sixty-eight patients were analyzed including 144 patients (99 women, 45 men) undergoing gastrointestinal malignancy surgery (group 1), 124 patients (28 women, 96 men) undergoing urologic malignancy surgery (group 2). We found differences in lymphocyte count, LMR, and PLR values between the two groups. We found that NLR, PLR, LMR, and RDW values, as well as the counts of neutrophils, lymphocytes, and platelets, can predict mortality at specific cut-off points. Furthermore, we also identified an association between NLR, PLR, RDW values, and the APACHE-II score with the length of ICU stay. There was a difference in lymphocyte count, LMR and PLR values between the two groups.

Conclusion: By utilizing cost-effective and practically applicable laboratory parameters, we can anticipate the mortality rates of patients following after cancer surgery. Patients predicted to have a high mortality rate can be followed more closely and comprehensively.

Keywords: Intensive care, lymphocyte-to-monocyte ratio, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, RDW

ÖZ

Amaç: Nötrofil, lenfosit, monosit, trombosit sayıları ve yeni enflamatuvar faktörler olarak nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), lenfosit-monosit oranı (LMR) ve kırmızı hücre dağılım genişliği (RDW) hastalıkların ortaya çıkması ve gelişmesinde önemli rol oynar. Bu çalışmada onkolojik cerrahi sonrası yoğun bakım ünitesine (YBÜ) yatırılan hastaların ameliyat öncesi NLR, PLR, LMR ve RDW değerleri ile yoğun bakım kalış süreleri ve mortalite oranları arasındaki ilişkinin araştırılması amaçlanmıştır. Ayrıca her iki grup arasında demografik ve klinik özellikler ile laboratuvar parametrelerinin karşılaştırılması da amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya onkolojik cerrahi sonrası YBÜ'de yatan hastalar dahil edildi. Hastalar gastrointestinal malignite (kolorektal, mide ve hepatoselüler) cerrahisi geçiren hastalar (grup 1) ve ürolojik malignite (böbrek, mesane ve prostat) cerrahisi geçiren hastalar (grup 2) olarak iki gruba ayrıldı. Demografik bilgiler (yaş ve cinsiyet), eşlik eden hastalıklar, nötrofil-lenfosit-trombosit sayıları, NLR-PLR-LMR-RDW değerleri, YBÜ'de kalış süresi, akut fizyoloji ve kronik sağlık değerlendirmesi-II (APACHE-II), Glasgow koma skalası ve mortalite oranları kaydedildi.

Bulgular: Gastrointestinal malignite cerrahisi geçiren 144 hasta (99 kadın, 45 erkek) (grup 1), ürolojik malignite cerrahisi geçiren 124 hasta (28 kadın, 96 erkek) (grup 2) olmak üzere 268 hasta analiz edildi. Her iki grup arasında lenfosit sayısı, LMR ve PLR değerlerinde fark olduğunu bulduk. NLR, PLR, LMR ve RDW değerleri ile nötrofil, lenfosit ve trombosit sayılarının belirli cut-off değerlerinde mortaliteyi tahmin edebildiğini bulduk. Ayrıca NLR, PLR, RDW değerleri ve APACHE-II skoru ile YBÜ'de kalış süresi arasında da ilişki tespit ettik.

Address for Correspondence: Yusuf Özgüner, Ankara Etlik City Hospital, Clinic of Anesthesiology and Reanimation, Ankara, Türkiye

Phone: +90 542 715 07 25 E-mail: y.ozguner@hotmail.com ORCID ID: orcid.org/0000-0002-9629-0246

Cite as: Özgüner Y, Altınsoy S. Relation of NLR, PLR, LMR and RDW with Mortality and Type of Surgery. Med J Bakirkoy 2023;19:352-359

Received: 21.08.2023
Accepted: 14.09.2023

Sonuç: Ucuz ve pratik uygulanabilen laboratuvar parametreleri kullanarak kanser cerrahisi sonrası takip edilen hastaların mortalite oranlarını tahmin edebiliriz. Yüksek mortalite beklenen hastaların daha yakın ve kapsamlı takibi sağlanabilir.

Anahtar Kelimeler: Yoğun bakım, lenfosit-monosit oranı, nötrofil-lenfosit oranı, platelet-lenfosit oranı, RDW

INTRODUCTION

Cancer is a significant contributor to global morbidity and mortality. Despite being a potential to be one of the most preventable and treatable chronic diseases, aggressive cancers may grow and spread so rapidly that they may metastasize before the cancer has been diagnosed (1). Cancers are the leading cause of death for individuals aged 45-64 and account for substantial healthcare expenditure (2). Thus, numerous biomarkers have been pursued to facilitate early cancer detection, prognosis assessment, and patient stratification based on treatment responsiveness (3,4).

Several studies have focused on the relationship between inflammation and cancer. Inflammation and activation of the immune system possess antitumor activity; however, they play a role in carcinogenesis, tumor growth, and the progression of human cancers (5). Platelets can stimulate tumor growth by increasing angiogenesis, microvascular permeability, and the extravasation of cancer cells (6). Neutrophil, lymphocyte, monocyte, thrombocyte counts, along with novel inflammatory factors, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and red cell distribution width (RDW) play an important role in the occurrence and development of diseases. Therefore, these hemogram based markers have been used in the diagnosis and prognosis of many different diseases (7,8). NLR and PLR are of a certain diagnostic value for frailty in hemodialysis patients and also associated with an unfavorable prognosis (9). PLR-NLR combination has an essential effect on the prognostic analysis of acute myocardial infarction (10). NLR and PLR values could reflect inflammatory response and disease activity in lupus patients (11). NLR, PLR and LMR values can be used as diagnostic and prognostic markers for cancer (12,13). It has also been reported that RDW values can be used to determine cancer progression (14). These parameters are markers of systemic inflammation and have been used to predict prognosis in many different types of cancer. As these blood tests are inexpensive and easy to detect, they have also been used in population-based screening for cancers (15,16).

In this study, it was aimed to investigate the relationship between preoperative NLR, PLR, LMR and RDW values of patients hospitalized in the intensive care unit (ICU) after oncological surgery, and the length of ICU stay and mortality rates. In addition, it will be investigated whether there is a difference in these parameters according to the type of cancer in patients.

METHODS

This study was approved by the Ankara Etlik City Hospital Clinical Research Ethics Committee (decision no: AEŞH-EK1-2023-279, date: 14.06.2023). Patients hospitalized in the ICU after oncological surgery between 1 October 2022 and 1 June 2023 were included in the study. Patients under the age of 18 and patients with missing data were excluded from the study. This research is a descriptive epidemiological study, and the population of the study consists of the records of postoperative patients hospitalized in the ICU of our hospital on the relevant dates. The aim was to reach all the patients included in the study.

Patient data were scanned and recorded retrospectively from hospital information system and ICU assessment forms. The patients were divided into two groups as patients undergoing gastrointestinal malignancy (colorectal, stomach and hepatocellular) surgery (group 1) and patients who had undergoing urologic malignancy (kidney, bladder and prostate) surgery (group 2). Information regarding demographics (age and gender), comorbidities, neutrophil-lymphocyte-platelet counts, NLR-PLR-LMR-RDW values, length of ICU stay, the acute physiology and chronic health evaluation-II (APACHE-II) score, Glasgow coma scale (GCS) and mortality rates were recorded.

NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. LMR was calculated by dividing the absolute lymphocyte count by the absolute monocyte count.

It was aimed to investigate the relationship between neutrophil-lymphocyte-platelet counts, NLR-PLR-LMR-RDW values and the length of intensive care and mortality rates. In addition, it was aimed to compare the demographic, clinical characteristics and laboratory parameters of the patients between both groups.

Statistical Analysis

All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). For

the normality check, the Shapiro-Wilks test was used. Data are given as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables. Between groups analysis of non-normally distributed continuous variables were performed with the Mann-Whitney U test. Between groups analysis of categorical variables were performed with the chi-square test or Fisher's Exact test. Spearman correlation test was used to evaluate the relationship between continuous variables. Mortality prediction performance of the measurements were assessed by using receiver operating characteristic (ROC) curve analysis. Optimal cut-off points were determined by using Youden index. Measurements of performance (sensitivity, specificity) were calculated according to determined cut-off points. Logistic regression analyses were performed to evaluate association between measurements and mortality. Multiple linear regression analysis were performed to determine the related factors with the length of ICU stay. While constructing the regression model, parameters that were significant in univariable analyses were included in multivariable analyses. Two-tailed p-values of less than 0.05 were considered statistically significant.

RESULTS

The study included 321 patients who were admitted to the ICU after oncological surgery between October 1, 2022, and June 1, 2023. Of these, 12 patients were excluded from the study because of missing data, 7 patients died in the first 24 hours, 26 patients were hospitalized for less than 24 hours, and 8 patients were transferred to other ICUs. As a result, 268 patients were analyzed including 144 patients (99 women, 45 men) undergoing gastrointestinal malignancy surgery (group 1), 124 patients (28 women, 96 men) undergoing urologic malignancy surgery (group 2) (Figure 1). The number of female patients in group 1 and the number of male patients in group 2 was higher and there was a statistical difference between them (p<0.001). The mean age of the patients was 66.73±12.48 years (group 1: 66.08±12.75; group 2: 67.49±12.16) years. There was no difference in the mean age between the two groups (p=0.358) (Table 1).

Demographic and clinical characteristics of the patients are listed in Table 1.

While the mean length of ICU stay was 2.21±2.46 days in group 1, it was 1.83±1.64 days in group 2. There was no difference in the length of ICU stay between the two groups (p=0.150) (Table 1).

Twenty seven patients (group 1: 19, group 2: 8) died in the ICU, 241 patients (group 1: 125, group 2: 116) were

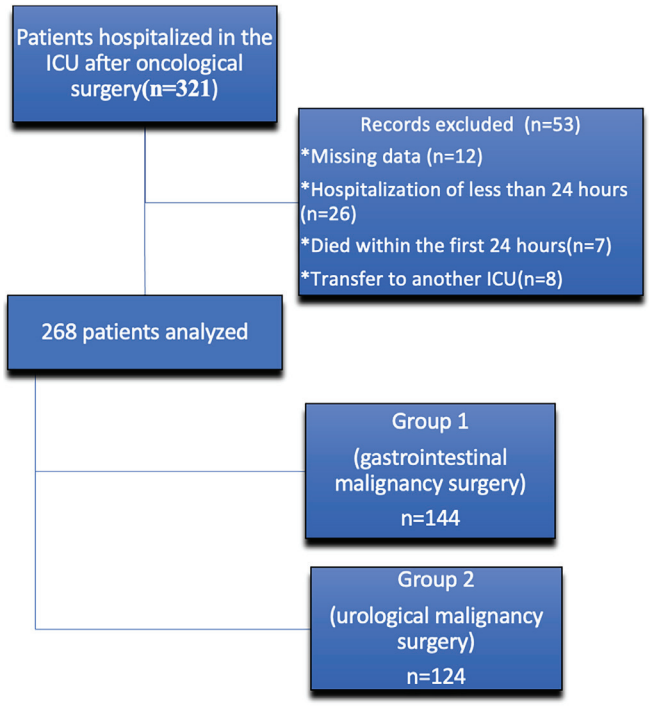

Figure 1. Flow chart of the patients
ICU: Intensive care unit

discharged from the ICU. When mortality rates were compared between the two groups, there was no statistically significant difference (p=0.067) (Table 1).

Comparisons between neutrophil/lymphocyte/monocyte/platelet counts and NLR/PLR/LMR/RDW values of the patients in the both groups are listed in Table 2.

The mean neutrophil count of the patients who died in the ICU was 8.86±2.88; lymphocyte count was 0.41±0.55; monocyte count was 0.68±0.49; platelet count was 197.51±130.1 and the mean NLR value was 30.03±15.33; PLR value was 627.52±409.65; LMR value was 1.10±1.21; RDW value was 61.35±10.69; APACHE-II score was 21.70±3.27; GCS was 13.33±2.11.

The mean neutrophil count of the patients discharged from the ICU was 5.64±3.09; lymphocyte count was 1.64±0.87; monocyte count was 0.69±0.58; and platelet count was 270.17±116.49 and the mean NLR value was 5.74±7.24; the PLR value was 228.49±193.42; the LMR value was 2.89±1.71; and the RDW value was 47.64±12.06; APACHE-II score was 14.15±5.13; GCS was 14.70±1.10.

While the neutrophil count and APACHE-II score, NLR, PLR, RDW values were higher in the patients who died in the ICU than the patients who were discharged from the ICU (p<0.001), the lymphocyte, platelet counts, GCS and LMR values were higher in the patients who were discharged

Table 1. Demographic data

	Group 1 (gastrointestinal malignancy surgery) n=144	Group 2 (urological malignancy surgery) n=124	p-value
Age (year)*	66.08±12.75	67.49±12.16	0.358
Sex (n) female/ male	99/45	28/96	**<0.001**
Length of ICU stay (day)*	2.21±2.46	1.83±1.64	0.150
APACHE-II score*	14.85±5.64	14.98±5.26	0.849
Glasgow coma scale*	14.46±1.59	14.68±0.83	0.157
Comorbidity			
COPD	49	43	0.911
CAD	55	65	***<0.05***
Cerebrovascular disease	23	23	0.577
Diabetes mellitus	57	47	0.778
Hypertension	47	39	0.836
Dementia/ Alzhemier	11	7	0.516
Renal disease	10	23	**<0.05**
Psychiatric disease	10	3	0.086
Rheumatological disease	4	1	0.234
Mechanical ventilation requirement (n)			
IMV/NIMV/SP	21/4/119	9/7/108	p=0.096
Result			
Exitus/discharge	19/125	8/116	p=0.067

APACHE-II: Acute physiology and chronic health evaluation-II, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation, SP: Spontane breathing
*Mean ± standard deviation, p<0.05 was considered significant

from the ICU than the patients who died (p<0.001). The monocyte count was similar in the patients who died and were discharged (p=0.972).

Multiple logistic regression analysis had revealed that high NLR [odds ratio (OR): 1.177, 95% confidence interval (CI): 1.072-1.293, p=0.001] and high APACHE-II score (OR: 1.349, 95% CI: 1.021 - 1.783, p=0.035) were independently associated with the mortality. In addition, low GCS (OR: 0.425, 95% CI: 0.232-0.778, p=0.006) and having chronic obstructive pulmonary disease (COPD) (OR: 27.288, 95% CI: 1.617-460.607, p=0.022) were independently associated with the mortality (Table 3).

Table 2. Comparisons of hemogram based markers between groups

	Group 1 (gastrointestinal malignancy surgery) n=144	Group 2 (urological malignancy surgery) n=124	p-value
Neutrophil ($\times10^3/\mu L$)*	5.76±2.94	6.19±3.51	0.276
Lymphocyte ($\times10^3/\mu L$)*	1.34±0.80	1.74±1	**<0.001****
Monocyte ($\times10^3/\mu L$)*	0.71±0.7	0.67±0.36	0.631
Platelets ($\times10^3/\mu L$)*	264.38±115.63	261.08±124.7	0.823
NLR*	9.06±12.28	7.17±9.56	0.167
PLR*	307.27±287.39	223.88±200.29	**<0.05****
LMR*	2.42±1.59	3.05±1.86	**<0.05****
RDW (fL)*	49.2±10.53	48.82±14.7	0.809

LMR: Lymphocyte-to-monocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, RDW: Red cell distribution width
*Mean ± standard deviation, **p<0.05 was considered significant

NLR had 92.6% sensitivity and 90.0% specificity to predict mortality for the cut of point of 14,50 (higher values represent mortality), also had the highest area under ROC curve [Area under ROC curve (AUC): 0.946 (95% CI: 0.903-0,989), p<0.001]. PLR had 77.8% sensitivity and 79.7% specificity to predict mortality for the cut-off point of 304.29 (higher values represent mortality) [AUC: 0.827 (95% CI: 0.736-0.919), p<0.001]. LMR had 70.4% sensitivity and 93.4% specificity to predict mortality for the cut-off point of 0.725 (lower values represent mortality) [AUC: 0.828 (95% CI: 0.733-0.924), p<0.001]. In addition, neutrophil, lymphocyte, and platelet counts and RDW value were statistically significant predictors of mortality at certain cut-off points (Table 4, Figure 2).

Multiple linear regression analysis revealed that APACHE-II score (p=0.042), RDW (p=0.030), NLR (p=0.016), PLR (p<0.001) were independently associated with increased length of ICU stay (Table 5).

DISCUSSION

In this study, we aimed to investigate the impact of hemogram-based markers on the length of ICU stay and mortality rates in patients hospitalized in the ICU after gastrointestinal and urological malignancy surgery. We observed that the lymphocyte count and LMR value were lower in group 1 when compared to group 2; conversely, the PLR value was higher. Additionally, we found that NLR, PLR,

Table 3. Significant factors independently associated with mortality, multiple logistic regression analysis

Variables	β coefficient	Standard error	Wald	df	p	Exp (β)	95.0% CI for Exp (β)	
Age (year)	-0.084	0.056	2.231	1.000	0.135	0.919	0.823	1.027
APACHE-II	0.300	0.142	4.441	1.000	**0.035***	1.349	1.021	1.783
Glasgow coma scale	-0.856	0.308	7.702	1.000	**0.006***	0.425	0.232	0.778
RDW	0.046	0.026	3.292	1.000	0.070	1.048	0.996	1.101
NLR	0.163	0.048	11.623	1.000	**0.001***	1.177	1.072	1.293
PLR	-0.001	0.001	0.217	1.000	0.641	0.999	0.997	1.002
LMR	-0.008	0.260	0.001	1.000	0.974	0.992	0.596	1.650
COPD	3.306	1.442	5.258	1.000	**0.022***	27.288	1.617	460.607
CAD	1.876	1.061	3.124	1.000	0.077	6.527	0.815	52.257
Dementia/Alzhemier	-0.155	1.214	0.016	1.000	0.898	0.856	0.079	9.255
Renal disease	0.592	0.914	0.420	1.000	0.517	1.808	0.301	10.846
Constant	1.141	5.023	0.052	1.000	0.820	3.128	-	-

Dependent variable: Mortality; Nagelkerke R^2=0.792; CI: Confidence Interval.

APACHE-II: Acute physiology and chronic health evaluation II, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, LMR: Lymphocyte-to-monocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, RDW: Red cell distribution width
*p<0.05 was considered significant

Table 4. Performance of variables to discriminate deceased cases

Variables	Cut-off	Sensitivity	Specificity	AUC (95% CI)	p-value
Neutrophil (×10³/μL)	>6.975	85.2	78.0	0.807 (0.717-0.897)	**<0.001***
Lymphocyte (×10³/μL)	<0.525	96.3	88.8	0.931 (0.862-1.000)	**<0.001***
Monocyte (×10³/μL)	-	-	-	0.501 (0.361-0.642)	0.981
Platelet (×10³/μL)	<156.00	55.6	89.6	0.689 (0.556-0.822)	**0.001***
RDW (fL)	>50.75	85.2	76.8	0.848 (0.760-0.937)	**<0.001***
NLR	>14.50	92.6	90.0	0.946 (0.903-0.989)	**<0.001***
PLR	>304.29	77.8	79.7	0.827 (0.736-0.919)	**<0.001***
LMR	<0.725	70.4	93.4	0.828 (0.733-0.924)	**<0.001***

AUC: Area under ROC curve, CI: Confidence intervals, LMR: Lymphocyte-to-monocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, RDW: Red cell distribution width
*p<0.05 was considered significant

LMR, and RDW values, as well as the counts of neutrophils, lymphocytes, and platelets, can predict mortality at specific cut-off points. Furthermore, we also identified an association between NLR, PLR, RDW values, and the APACHE-II score with the length of ICU stay.

Grossman et al. (17) reported that severe treatment-related lymphopenia, observed after initiating chemoradiation in patients with solid tumors, was independently associated with shorter survival from tumor progression. Péron et al. (18) reported that an increased incidence of lymphopenia was observed in advanced and metastatic cancers. In our study, we found that the lymphocyte count in patients operated for colorectal, gastric, pancreatic, and hepatocellular cancer was lower than the lymphocyte count in patients operated for kidney, bladder, and prostate cancer. We think, the reason for this situation is that patients who had undergone gastrointestinal surgery had more advanced cancer and had received preoperative chemotherapy/radiotherapy. We observed that there was a difference in LMR and PLR values between the two groups because of the low lymphocyte count.

Yang et al. (19) reported that elevated neutrophil counts independently predicted shorter survival among patients with metastatic colon cancer. Dou et al. (20) reported that

there is a relationship between low lymphocyte counts and inadequate response in rectal cancer cases. In our study, in line with the current literature, we found an increase in mortality among patients with high neutrophil counts and low lymphocyte counts.

Feliciano et al. (21) reported that there is a positive correlation between NLR value and sarcopenia and this is also associated with mortality. Cupp et al. (22) reported that there is a relationship between NLR value and mortality in cases of immunotherapy-treated urinary system cancers. Yao et al. (23) reported that NLR and PLR values were associated with mortality in patients with COPD. Capone et al. (24) also reported that there is a relationship between NLR value and survival in advanced cancer patients. In our study, we observed that the NLR, PLR, and RDW values were higher, while the LMR values were lower in patients who died in the ICU. Additionally, we found that NLR, PLR, LMR, RDW values, as well as neutrophil, lymphocyte, and platelet counts, could predict mortality at specific cutoff points. Our findings are consistent with the existing literature.

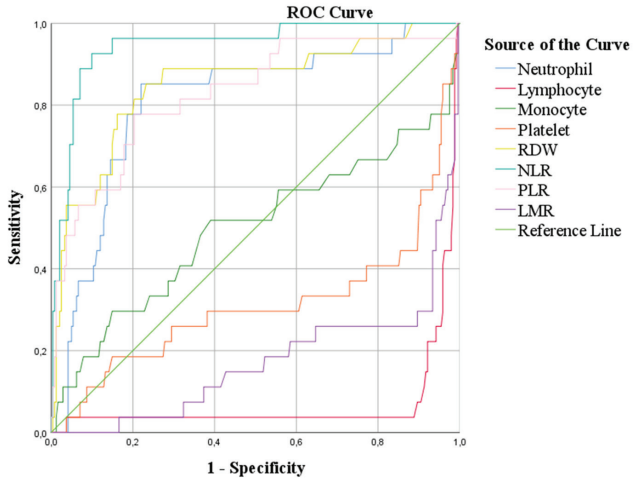

Figure 2. ROC curves of the measurements to predict mortality
NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, RDW: Red cell distribution width, LMR: Lymphocyte-to-monocyte ratio, ROC: Receiver operating characteristic

Miyamoto et al. (25) reported that the preoperative NLR is a useful predictor in gastric cancer patients and there is a relationship between NLR value and the prognosis. Dell'Aquila et al. (26) reported that their study confirmed the prognostic role of NLR in colorectal cancer patients. Chang et al. (27) found that preoperative albumin and LMR values were associated with postoperative prognosis in renal cell cancer patients. Chen et al. (28) demonstrated the close relationship between NLR, LMR, PLR values, and the grade and recurrence of bladder cancer. They also suggested that the combination of these three factors had the potential to aid in prognostic evaluation of bladder cancer. Wang et al. (29) reported a relationship between NLR value and length of hospital stay in patients with COPD. In our study, which included patients who had experienced gastrointestinal and urological malignancies, we found that NLR, PLR, and RDW values were associated with the length of ICU stay. Our findings are consistent with the existing literature.

Godinjak et al. (30) reported that the APACHE-II score can be used to predict mortality in the ICU. Cao et al. (31)

Table 5. Significant risk factors independently associated with length of ICU stay, multiple linear regression analysis

	Unstandardized β	Standard error	Standardized β	t	p	95.0% Confidence interval for β	
(Constant)	-0.915	1.509	-	-0.607	0.545	-3.886	2.056
Age	-0.017	0.010	-0.101	-1.751	0.081	-0.037	0.002
APACHE-II	0.054	0.027	0.139	2.040	**0.042***	0.002	0.106
GCS	0.040	0.081	0.025	0.496	0.620	-0.120	0.200
Neutrophil	0.046	0.044	0.069	1.042	0.299	-0.041	0.132
Lymphocyte	0.258	0.178	0.112	1.452	0.148	-0.092	0.608
Platelet	-0.001	0.001	-0.076	-1.182	0.239	-0.004	0.001
RDW	0.017	0.008	0.103	2.177	**0.030***	0.002	0.033
NLR	0.044	0.018	0.228	2.418	**0.016***	0.008	0.079
PLR	0.003	0.001	0.412	4.907	**<0.001***	0.002	0.005
LMR	-0.034	0.076	-0.028	-0.447	0.655	-0.184	0.116

APACHE-II: Acute physiology and chronic health evaluation II, GCS: Glasgow coma scale, LMR: Lymphocyte-to-monocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, RDW: Red cell distribution width
*$p<0.05$ was considered significant.
Dependent variable: Length of ICU stay; $R^2=0.520$; $F=18.212$

reported that in critically ill patients, the APACHE-II score, in conjunction with lactate levels, provides a better prediction of mortality. Ahmadi et al. (32) have also reported that the GCS is associated with mortality in patients with traumatic brain injury. In our study, we found a relationship between mortality rate and APACHE-II score, GCS. Furthermore, we found that the APACHE-II score is also associated with the length of ICU stay. We observed that our data were consistent with studies in the literature.

There are certain limitations to this study. First, our patient group operated for cancer was limited to gastrointestinal and urological cancer patients in our hospital. Since many different cancer surgeries such as lung cancer, larynx and nasopharyngeal cancer, orthopedic tumor surgeries were not operated in our hospital, we could not include the patients operated for different cancer types in our study group. Second, it was a single-center and retrospective study and this limited the number of patients.

CONCLUSION

The use of many different biomarkers in order determine the early diagnosis, treatment and prognosis of cancers is still being investigated today. Alterations in neutrophil, lymphocyte, monocyte, and platelet counts, as well as associated ratios, serve as indicators of systemic inflammation and are used to predict diagnosis, treatment and prognosis in many different types of cancer. These hemogram based markers are cost-effective and routinely requested in all preoperative patients. By utilizing cost-effective and practically applicable laboratory parameters, we can anticipate the mortality rates of patients following after cancer surgery. Patients predicted to have a high mortality rate can be followed more closely and comprehensively.

ETHICS

Ethics Committee Approval: This study was approved by the Ankara Etlik City Hospital Clinical Research Ethics Committee (decision no: AEŞH-EK1-2023-279, date: 14.06.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Y.Ö., S.A., Concept: Y.Ö., S.A., Design: Y.Ö., S.A., Data Collection or Processing: Y.Ö., S.A., Analysis or Interpretation: Y.Ö., S.A., Literature Search: Y.Ö., Writing: Y.Ö., S.A.

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

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

REFERENCES

1. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated Projection of US Cancer Incidence and Death to 2040. JAMA Netw Open 2021;4:e214708.
2. Dieleman JL, Baral R, Birger M, Bui AL, Bulchis A, Chapin A, et al. US Spending on Personal Health Care and Public Health, 1996-2013. JAMA 2016;316:2627-46.
3. Zou J, Wang E. Cancer Biomarker Discovery for Precision Medicine: New Progress. Curr Med Chem 2019;26:7655-71.
4. Wu L, Qu X. Cancer biomarker detection: recent achievements and challenges. Chem Soc Rev 2015;44:2963-97.
5. Dmitrieva OS, Shilovskiy IP, Khaitov MR, Grivennikov SI. Interleukins 1 and 6 as Main Mediators of Inflammation and Cancer. Biochemistry (Mosc) 2016;81:80-90.
6. Sabrkhany S, Griffioen AW, Oude Egbrink MG. The role of blood platelets in tumor angiogenesis. Biochim Biophys Acta 2011;1815:189-96.
7. Aygun K, Gokdemir O, Sisman AR, Demir T. The Relationship Between Hypothyroidism-Induced Autoantibodies, TSH Levels, and RDW, as an Inflammation Marker. J Cukurova Anesth Surg 2023;6:56-66.
8. Honca T, Parlak A, Hakan Ö, Sarer E, Honca M. Determination of the effects of inflammatory markers on mortality in intensive care patients. J Cukurova Anesth Surg 2022;5:389-96.
9. Wang J, Huang L, Xu M, Yang L, Deng X, Li B. Study on the Clinical Implications of NLR and PLR for Diagnosing Frailty in Maintenance Hemodialysis Patients and Their Correlations with Patient Prognosis. J Healthc Eng 2022;2022:1267200.
10. Liu J, Ao W, Zhou J, Luo P, Wang Q, Xiang D. The correlation between PLR-NLR and prognosis in acute myocardial infarction. Am J Transl Res 2021;13:4892-9.
11. Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Mod Rheumatol 2016;26:372-6.
12. Li P, Li H, Ding S, Zhou J. NLR, PLR, LMR and MWR as diagnostic and prognostic markers for laryngeal carcinoma. Am J Transl Res 2022;14:3017-27.
13. Uzunoğlu H, Kaya S. Predictive Value of Preoperative NLR and PLR in Short-term Survival in Rectal Cancer. Kocaeli Med J 2022;11:136-43.
14. Hu L, Li M, Ding Y, Pu L, Liu J, Xie J, et al. Prognostic value of RDW in cancers: a systematic review and meta-analysis. Oncotarget 2017;8:16027-35.
15. Mandaliya H, Jones M, Oldmeadow C, Nordman II. Prognostic biomarkers in stage IV non-small cell lung cancer (NSCLC): neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR) and advanced lung cancer inflammation index (ALI). Transl Lung Cancer Res 2019;8:886-94.
16. Fang T, Wang Y, Yin X, Zhai Z, Zhang Y, Yang Y, et al. Diagnostic Sensitivity of NLR and PLR in Early Diagnosis of Gastric Cancer. J Immunol Res 2020;2020:9146042.
17. Grossman SA, Ellsworth S, Campian J, Wild AT, Herman JM, Laheru D, et al. Survival in Patients With Severe Lymphopenia Following Treatment With Radiation and Chemotherapy for Newly Diagnosed Solid Tumors. J Natl Compr Canc Netw 2015;13:1225-31.
18. Péron J, Cropet C, Tredan O, Bachelot T, Ray-Coquard I, Clapisson G, et al. CD4 lymphopenia to identify end-of-life metastatic cancer patients. Eur J Cancer 2013;49:1080-9.

19. Yang J, Guo X, Wang M, Ma X, Ye X, Lin P. Pre-treatment inflammatory indexes as predictors of survival and cetuximab efficacy in metastatic colorectal cancer patients with wild-type RAS. Sci Rep 2017;7:17166.
20. Dou X, Wang RB, Yan HJ, Jiang SM, Meng XJ, Zhu KL, et al. Circulating lymphocytes as predictors of sensitivity to preoperative chemoradiotherapy in rectal cancer cases. Asian Pac J Cancer Prev 2013;14:3881-5.
21. Feliciano EMC, Kroenke CH, Meyerhardt JA, Prado CM, Bradshaw PT, Kwan ML, et al. Association of Systemic Inflammation and Sarcopenia With Survival in Nonmetastatic Colorectal Cancer: Results From the C SCANS Study. JAMA Oncol 2017;3:e172319.
22. Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med 2020;18:360.
23. Yao C, Liu X, Tang Z. Prognostic role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio for hospital mortality in patients with AECOPD. Int J Chron Obstruct Pulmon Dis 2017;12:2285-90.
24. Capone M, Giannarelli D, Mallardo D, Madonna G, Festino L, Grimaldi AM, et al. Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. J Immunother Cancer 2018;6:74.
25. Miyamoto R, Inagawa S, Sano N, Tadano S, Adachi S, Yamamoto M. The neutrophil-to-lymphocyte ratio (NLR) predicts short-term and long-term outcomes in gastric cancer patients. Eur J Surg Oncol 2018;44:607-12.
26. Dell'Aquila E, Cremolini C, Zeppola T, Lonardi S, Bergamo F, Masi G, et al. Prognostic and predictive role of neutrophil/lymphocytes ratio in metastatic colorectal cancer: a retrospective analysis of the TRIBE study by GONO. Ann Oncol 2018;29:924-30.
27. Chang Y, An H, Xu L, Zhu Y, Yang Y, Lin Z, et al. Systemic inflammation score predicts postoperative prognosis of patients with clear-cell renal cell carcinoma. Br J Cancer 2015;113:626-33.
28. Chen H, Wu X, Wen Z, Zhu Y, Liao L, Yang J. The Clinicopathological and Prognostic Value of NLR, PLR and MLR in Non-Muscular Invasive Bladder Cancer. Arch Esp Urol 2022;75:467-71.
29. Wang H, Yang T, Yu X, Chen Z, Ran Y, Wang J, et al. Risk Factors for Length of Hospital Stay in Acute Exacerbation Chronic Obstructive Pulmonary Disease: A Multicenter Cross-Sectional Study. Int J Gen Med 2022;15:3447-58.
30. Godinjak A, Iglica A, Rama A, Tančica I, Jusufović S, Ajanović A, et al. Predictive value of SAPS II and APACHE II scoring systems for patient outcome in a medical intensive care unit. Acta Med Acad 2016;45:97-103.
31. Cao Y, Yao S, Shang J, Ping F, Tan Q, Tian Z, et al. The combination of lactate level, lactate clearance and APACHE II score better predicts short-term outcomes in critically Ill patients: a retrospective cohort study. BMC Anesthesiol 2022;22:382.
32. Ahmadi S, Sarveazad A, Babahajian A, Ahmadzadeh K, Yousefifard M. Comparison of Glasgow Coma Scale and Full Outline of UnResponsiveness score for prediction of in-hospital mortality in traumatic brain injury patients: a systematic review and meta-analysis. Eur J Trauma Emerg Surg 2023;49:1693-706.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:360-364
DOI: 10.4274/BMJ.galenos.2023.2022.11-10

Research

Serum Vitamin D Levels and Food Sensitization in Atopic Dermatitis: A Single-center Study

Atopik Dermatitli Olgularda Serum D Vitamini Düzeyi ve Besin Duyarlanması: Tek Merkezli Çalışma

Ömer Akçal[1], İlke Taşkırdı[2], Abdullah Sert[3], Yıldırım Mehmet Ramazanoğlu[3], Erkan Can[3], Bilge Tanyeri Bayraktar[4]

[1]Biruni University Hospital, Department of Pediatrics, Division of Immunology and Allergy, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital, Clinic of Pediatrics, Division of Immunology and Allergy, İzmir, Türkiye
[3]Biruni University Hospital, Department of Pediatrics, İstanbul, Türkiye
[4]Biruni University Hospital, Department of Pediatrics, Division of Neonatology, İstanbul, Türkiye

ABSTRACT

Objective: Atopic dermatitis (AD) is a chronic, itchy, recurrent, and recurrent inflammatory skin disease that affects 2-20% of the population, especially in childhood. Its pathophysiology is complex and occurs as a result of genetic, immunological, and environmental factors, especially epithelial-barrier dysfunction. We determined the frequency of food sensitization and vitamin D deficiency in patients with AD.

Methods: This cross-sectional retrospective study was conducted by examining the files of patients who were admitted to the pediatrics allergy and immunology outpatient clinic with AD. A total of 72 patients with eczema were included in the study.

Results: 37.5% (n=27) of the patients were girls. The mean age was 3.8±3.6 years. Food sensitization was proven in 40.2% (n=29) of all cases included in the study. Vitamin D deficiency was found in 30.6% (n=22) of the cases. Serum 25-hydroxyvitamin D3 levels were found to be lower in the patient group than in the control group. The limitation of our study is that it was retrospective and blood tests could not be re-evaluated after treatment in all patients.

Conclusion: In patients with AD, serum vitamin D levels were significantly lower. We examined vitamin D deficiency in AD patients who applied to us as a clinical team. According to our study, we can say that both food sensitization and vitamin D deficiency should be investigated in AD patients.

Keywords: D vitamine deficiency, food allergy, eczema, atopic dermatitis

ÖZ

Amaç: Atopik dermatit (AD), özellikle çocukluk çağında, nüfusun %2-20'sini etkileyen, kronik, kaşıntılı ve tekrarlayan enflamatuvar bir deri hastalığıdır. Patofizyolojisi net olmamakla beraber, başta epitel bariyer disfonksiyonu olmak üzere genetik, immünolojik ve çevresel faktörlerin bir sonucu olarak gelişmektedir. Çalışmamızda AD olgularında besin duyarlılığı ve D vitamini eksikliği sıklığını saptamayı amaçladık.

Gereç ve Yöntem: Bu kesitsel retrospektif çalışma, hastanemizin çocuk alerji ve immünoloji polikliniğinde atopik dermatit tanısı ile izlenen hastaların dosyaları incelenerek yapıldı. Çalışmaya toplam 72 AD hastası dahil edildi.

Bulgular: Hastaların %37,5'i (n=27) kızdı. Ortalama yaş 3,8±3,6 idi. Çalışmaya dahil edilen tüm olguların %40,2'sinde (n=29) besin duyarlılığı tespit edildi. Olguların %30,6'sında (n=22) D vitamini eksikliği saptandı. Serum 25-hydroksivitamin D3 düzeyleri hasta grubunda kontrol grubuna göre daha düşük bulundu. Çalışmamızın kısıtlılığı retrospektif olması ve tüm hastalarda tedavi sonrası tekrar tetkik edilememesidir.

Sonuç: AD tanılı hastalarda serum D vitamini düzeyleri anlamlı olarak düşük bulundu. Klinik olarak AD tanısı ile izlenen hastalarda D vitamini eksikliği değerlendirilmektedir. Çalışmamızdaki istatistiksel sonuçlara göre AD tanılı olgularda hem besin duyarlanması hem de D vitamini eksikliği yönünden değerlendirilmesi gerektiğini söyleyebiliriz.

Anahtar Kelimeler: D vitamini eksikliği, besin alerjisi, egzama, atopik dermatit

Address for Correspondence: İlke Taşkırdı, University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital, Clinic of Pediatrics, Division of Immunology and Allergy, İzmir, Türkiye
Phone: +90 532 203 08 46 E-mail: ilke_66@icloud.com ORCID ID: orcid.org/0000-0001-9326-2541

Cite as: Akçal Ö, Taşkırdı İ, Sert A, Ramazanoğlu YM, Can E, Tanyeri Bayraktar B. Serum Vitamin D Levels and Food Sensitization in Atopic Dermatitis: A Single-center Study. Med J Bakirkoy 2023;19:360-364

Received: 30.11.2022
Accepted: 11.04.2023

INTRODUCTION

Atopic dermatitis (AD) is a chronic, itchy, recurrent, and relapsing inflammatory skin disease that affects 2-20% of the population and is especially encountered in childhood. The pathophysiology is complex and occurs as a result of genetic, immunological, and environmental factors, especially epithelial-barrier dysfunction. Concomitant food allergy is observed in approximately 30% of AD cases (1-4).

Apart from all these, vitamin D deficiency among etiological factors and even vitamin replacement among treatment approaches has been the subject of discussion for a long time. Vitamin D is a special vitamin for the immune system that has hormone-like properties, bioactive metabolites, and acts by binding to nuclear hormone receptors in different tissues and cells. Vitamin cholecalciferol (Pre-D3) is synthesized in the skin from 7-dehydrocholesterol due to sunlight, especially ultraviolet B radiation (270-300 nm wavelengths) (5). Pre-D3 is then converted to 25-hydroxyvitamin D3 [25(OH)-D3] by 25-alpha-hydroxylase in the liver, which is the main metabolite in the circulation and can alternatively be consumed by nutrition. Finally, D3 and its most physiologically active metabolite, 1.25-dihydroxy D3 (calcitriol), are mainly produced in the kidneys by 1-alpha-hydroxylase (6,7). Calcitriol plays an immunoregulatory role by binding to the vitamin D receptor and acting on immune cells in an autocrine or paracrine manner (6). Epithelial cells, antigen-presenting cells, lymphocytes, mast cells, eosinophils, and innate lymphoid cells play a role in AD immunopathogenesis. T helper 2 (TH2) differentiation is stimulated by alarmins produced by epithelial cells. While there is TH2 dominance in the early period, other lymphocyte subgroups and the cytokines they produce come to the fore in the chronic phase along with TH2. In the acute phase, IL-4, IL-5, and IL-13 are produced from TH2 lymphocytes. Calcitriol, on the other hand, stimulates T-regulatory (Treg) cell differentiation and thus helps suppress the increased and uncontrolled inflammation observed in AD (5-7). Therefore, we hypothesized that vitamin D deficiency may be more common in patients with AD than in the normal population. There are not many studies in the literature examining both vitamin D deficiency and food sensitization in AD cases. In our study, we aimed to comparatively evaluate vitamin D levels in AD patients with and without food sensitization.

METHODS

The study was approved by the Biruni University Non-invasive Research Ethics Committee (decision no: 2021/64-6, approval date: 17.12.2021). Informed consent was obtained from all participants. This cross-sectional retrospective study was conducted by examining the files of patients who were referred to our pediatrics allergy and immunology outpatient clinic because of persistent or recurrent eczema.

Patients

The study started by examining the files of patients who were diagnosed with eczema among the patients who applied to our hospital between August 2021 and February 2022. During this period, 250 eczema cases were detected, and it was noted that 113 cases were referred to the pediatric allergy and immunology outpatient clinic. Upon examining the files, 137 patients were excluded from the study because they did not come for follow-up, and 41 patients were excluded because their file data was not complete (Figure 1). As a result, it was found appropriate to include 72 patients in the study. A control group comprised healthy children who applied to the pediatric outpatient clinic for routine control or check-up. Children with serum 25(OH)D3 levels and blood test results were selected. Eighty healthy children of equivalent age and gender were randomized as the control group. Later the same parameters were compared between the patient and control groups.

Study Design

Demographic data, gender, age, blood tests, absolute eosinophil count (AEC), serum 25(OH)D3 levels, presence of additional atopic disease, specific and total IgE levels, skin prick test results, examination findings, treatments applied, and responses given to treatment were noted from patient files. Values with serum 25(OH)D3 levels below 20 ng/mL were accepted as "vitamin D deficiency". Cases with proven food sensitivity by serum-specific IgE and skin prick test. Total IgE levels below 100 kU/L were considered normal. Food-specific IgE levels below 0.35 kUA/L were considered negative. Histamine (10 mg/mL) was used as the positive control and saline as the negative control in the skin prick test panel. An induration greater than 3 mm was considered positive. Patients with a SCORAD index below 25 were considered "mild", between 25 and 50 "moderate", and above 25 "severe".

Statistical Analysis

Data were analyzed using SPSS statistical software, version 22 (SPSS Inc, Chicago, IL). Continuous variables are expressed as mean ± standard deviation and categorical variables as number (%). For comparisons, we used independent t-test and One-Way ANOVA for continuous variables and chi-square test for categorical variables. Pearson's test was used for correlation analysis. $P<0.05$ was considered statistically significant.

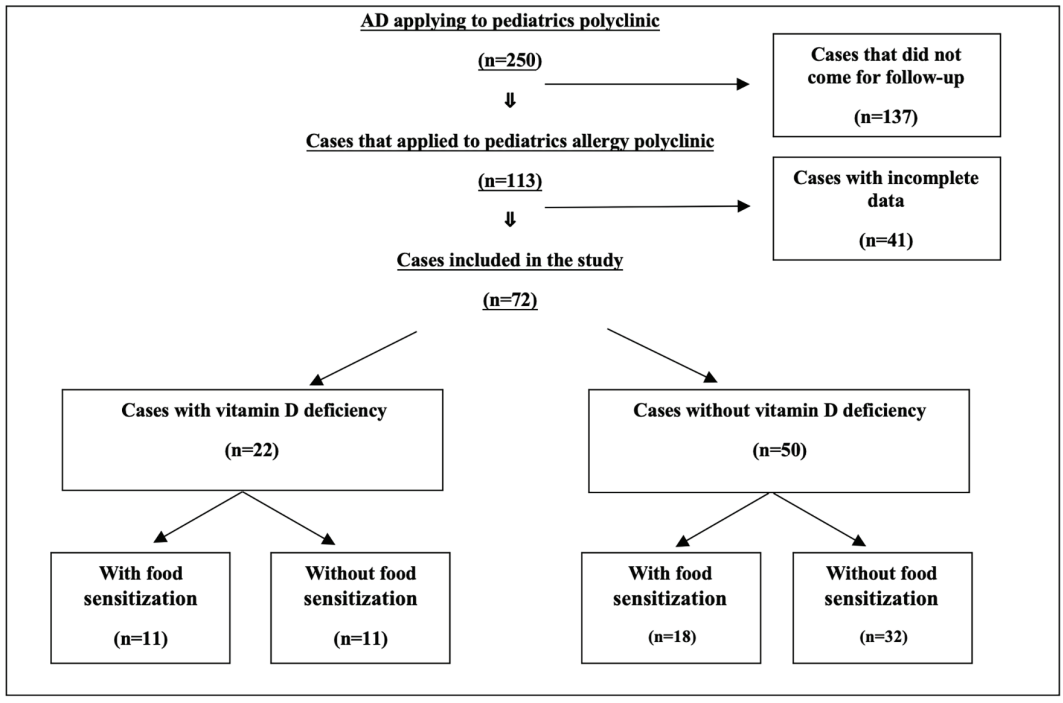

Figure 1. Study design

RESULTS

37.5% (n=27) of 72 patients included in the study were girls. The mean age was 3.8±3.6 years. When the file records of the patients were examined, the mean AEC was 632±711,4/mm^3, and the mean total IgE level was 134 kU/L. The highest AEC was 4080/mm^3, whereas the highest IgE value was 2000 kU/L. The mean AEC of the patient group was higher than that of the control group and was statistically significant (p<0.0001). The mean serum 25(OH)D3 level was 20.3±9.2 ng/mL. Vitamin D deficiency was detected in 30.6% (n=22) of the patients. In the control group, vitamin D deficiency was detected in 12.5% (n=10). It was statistically significant (p<0.0001). A comparison of the patient and control groups is given in Table 1.

The comparison according to the presence of vitamin D deficiency and food sensitization in the patient group is shown in Table 2. When the cases with vitamin D deficiency were compared according to gender, no significant difference was found (p=0.265). While food sensitization was observed in half of these cases (n=11), no food sensitization was observed in the other half. Food sensitization was proven in 40.2% (n=29) of all patients included in the study. When vitamin D deficiency was compared between patients with and without food sensitization, no statistically significant difference was found (p=0.921). When the total IgE level was compared between those with and without vitamin D deficiency, no statistically significant difference was found (p=0.48). There was a statistically significant difference in male gender between patients with and without food sensitization (p=0.006). Patients were compared according to the SCORAD index. Serum 25(OH)D3 levels and eosinophil counts were evaluated. There was a statistically significant difference between the groups, and the results are shown in Table 3.

Table 1. Comparison of study groups

	Patients (n=72)	Control (n=80)	p-value
Gender			
Female (n, %)	27 (37.5%)	23 (28.8%)	0.252
Male (n, %)	45 (62.5%)	57 (71.2%)	
Age (years, mean ± SD)	3.8±3.6	3.5±2.8	0.563
25(OH)D3 (ng/mL, mean ± SD)	20.3±9.2	29.3±6.7	**<0.0001**
Eosinophil (count/mm^3, mean ± SD)	632±711.4	120±169.5	**<0.0001**

SD: Standard deviation, 25(OH)D3: 25-hydroxyvitamin D3

DISCUSSION

Serum 25(OH)D3 levels have been examined in different patient groups in various scientific studies (8-11). Calcitriol increases its affinity and migration to cutaneous tissue by increasing the expression of C-C chemokine receptor type 10 in T lymphocytes. The calcitriol produced suppresses

Table 2. Comparison of patient groups

	D vitamin deficiency		
	Positive (n=22)	Negative (n=50)	p-value
	n (30.6%)	n (69.4%)	
Gender			
Female	9 (40%)	18 (36%)	0.692
Male	13 (60%)	32 (64%)	
Age, years	4.5±3.6	3.5±3.6	0.29
Food sensitization			
Positive	11 (50%)	18 (36%)	0.265
Negative	11 (50%)	32 (64%)	
Eosinophil (count /mm^3), mean ± SD	551.3±588.2	667.4±762.1	0.52
Total IgE (IU/mL), mean ± SD	128.6±186	129.8±317	0.98
	Food sensitization		
	Positive (n=29)	Negative (n=43)	p-value
	n (%)	n (%)	
Gender			
Female	5 (17%)	22 (51%)	**0.006**
Male	24 (83%)	21 (49%)	
Age, years	2.7±2.6	4.5±4	**0.03**
25(OH)D (ng/mL), mean ± SD	19.1±10.7	21.2±8.1	0.34
Eosinophil (count /mm^3), mean ± SD	791.5±830.8	524.3±604.9	0.11
Total IgE (IU/mL), mean ± SD	150.2±347	98.7±138	0.38

SD: Standard deviation, 25(OH)D3: 25-hydroxyvitamin D3

TH1 differentiation in T lymphocytes, while inducing differentiation in the Treg cell direction. It also activates tolerogenic dendritic cells in skin tissue (6,7,11,12). In line with the basic information about this immune system, we can say that vitamin D plays an important immunoregulatory role in chronic cutaneous inflammation such as AD. Therefore, we evaluated the 25(OH)D3 levels in our patients with AD. There was statistically significant eosinophilia in our patients with severe eczema. Serum 25(OH)D3 levels were also significantly lower in these patients. We know that the number of eosinophils bound to IL-4 and IL-5 produced by TH2 cells increases. Vitamin D deficiency may have led to decreased T regulatory cell differentiation and increased TH2 differentiation. We hypothesized that vitamin D deficiency may also facilitate eosinophilia and food sensitization.

While the mean serum 25(OH)D3 level of our study subjects (n=72) was 20.3±9.2 ng/mL, Galli et al. (13) found (n=89) 48.3±40.6 ng/mL in their patients and Lara-Corrales et al. (14) found (n=77) 62.6±27.8 nmol/L in the study they conducted. Tromp et al. (15) found that low vitamin D levels were associated with increased eczema in their cohort study. In our study, we discussed the frequency of food sensitization and vitamin D deficiency in patients with eczema.

There is still no consensus on the optimal serum 25(OH)D3 vitamin level (15). As a clinical team, we analyzed vitamin D deficiency and food sensitivity in patients with eczema. In our study, eleven of the eczema cases had both vitamin D deficiency and food sensitization.

Galli et al. (13) included 89 eczema cases in their study, and the median age was reported to be 68 months. In this study, patients were categorized into two groups: susceptible with serum IgE levels above 40 UI/mL and non-sensitive with serum IgE levels below 40 IU/mL. 57% of the cases were accepted as sensitive. The food sensitization rate was found to be 20.2% (n=18). When compared with this study, the rate of food sensitization in our study was higher,

Table 3. Comparison of patient groups according to SCORAD index

	Mild (n=35)	Moderate (n=29)	Severe (n=8)	p-value
Gender				
Female (n, %)	13 (37.1%)	10 (34.4%)	4 (50%)	0.72
Male (n, %)	22 (62.9%)	19 (65.6%)	4 (50%)	
Eosinophil (count/mm^3, mean ± SD)	451.8±373.8	551.3±587.2	1712.5±1045.8	**<0.0001***
25(OH)D3 (ng/mL, mean ± SD)	24.9±8.6	17.3±6.8	11.3±9.2	**<0.0001***

*Post-hoc analyzed with tukey test: For eosinophil mild versus modarete p=0.79; mild versus severe p<0.0001; moderate versus severe p<0.0001. For 25(OH)D3 mild versus modarete p=0.001; mild versus severe p<0.0001; moderate versus severe p=0.154
SD: Standard deviation, 25(OH)D3: 25-hydroxyvitamin D3

quantitatively 40.2% (n=29). However, we grouped the cases that we considered sensitive not only by looking at the IgE level but also according to the results of the food-specific IgE skin prick test. While the mean total IgE value of the case group with food sensitivity in the study of Galli et al. (13) was 577.0±994 kU/L and the mean vitamin D level was 48±41.6 ng/mL, the mean total IgE value of our cases with food sensitization accompanied was 150.2±347 kU/L and their mean vitamin D level was 19.1±10.7 ng/mL.

Patients with food sensitization had a higher mean AEC than those without food sensitization. In case of vitamin D deficiency, it can be predicted that a predisposition may develop to hypersensitivity response or autoimmunity. Various scientific studies have shown that calcitriol replacement may be clinically beneficial for the treatment of inflammatory and autoimmune diseases (5,6,12,16). There is no definite consensus regarding the use of 25(OH) D3 replacement as a treatment (17-19). Kim et al. (17) suggested in their meta-analysis that serum 25(OH)D3 levels are important for the treatment of AD. In this meta-analysis, a significant difference was observed between serum 25(OH)D3 levels when the patient and control groups were compared. Detection of vitamin D deficiency and vitamin D replacement in patients with eczema may benefit treatment. However, prospective studies are required to evaluate the efficacy of vitamin D replacement in treatment.

The limitation of our study is that it was retrospective and blood tests could not be re-evaluated after treatment in all patients. Therefore, serum 25(OH)D3 levels should be checked again after treatment.

CONCLUSION

In patients with severe eczema, serum vitamin D levels were significantly lower. We examined vitamin D deficiency in eczema patients who applied to us as a clinical team. According to our study, both food sensitization and vitamin D deficiency should be investigated in patients with eczema.

Acknowlegements: The authors acknowledge the physicians and patients associated with this study.

ETHICS

Ethics Committee Approval: The study was approved by the Biruni University Non-invasive Research Ethics Committee (decision no: 2021/64-6, approval date: 17.12.2021).

Informed Consent: Retrospective study.

Authorship Contributions

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

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. David Boothe W, Tarbox JA, Tarbox MB. Atopic Dermatitis: Pathophysiology. Adv Exp Med Biol 2017;1027:21-37.
2. Avena-Woods C. Overview of atopic dermatitis. Am J Manag Care 2017;23(8 Suppl):115-23.
3. Strathie Page S, Weston S, Loh R. Atopic dermatitis in children. Aust Fam Physician 2016;45:293-6.
4. Domínguez O, Plaza AM, Alvaro M. Relationship Between Atopic Dermatitis and Food Allergy. Curr Pediatr Rev 2020;16:115-22.
5. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients 2013;5:2502-21.
6. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol 2008;8:685-98.
7. Aranow C. Vitamin D and the immune system. J Investig Med 2011;59:881-6.
8. Chau YY, Kumar J. Vitamin D in chronic kidney disease. Indian J Pediatr 2012;79:1062-68.
9. Chesdachai S, Tangpricha V. Treatment of vitamin D deficiency in cystic fibrosis. J Steroid Biochem Mol Biol 2016;164:36-9.
10. Bizzaro G, Antico A, Fortunato A, Bizzaro N. Vitamin D and Autoimmune Diseases: Is Vitamin D Receptor (VDR) Polymorphism the Culprit? Isr Med Assoc J 2017;19:438-43.
11. Kulda V. [Vitamin D metabolism]. Vnitr Lek 2012;58:400-4.
12. van Etten E, Mathieu C. Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts. J Steroid Biochem Mol Biol 2005;97:93-101.
13. Galli E, Rocchi L, Carello R, Giampietro PG, Panei P, Meglio P. Serum Vitamin D levels and Vitamin D supplementation do not correlate with the severity of chronic eczema in children. Eur Ann Allergy Clin Immunol 2015;47:41-7.
14. Lara-Corrales I, Huang CM, Parkin PC, Rubio-Gomez GA, Posso-De Los Rios CJ, Maguire J, et al. Vitamin D Level and Supplementation in Pediatric Atopic Dermatitis: A Randomized Controlled Trial. J Cutan Med Surg 2019;23:44-9.
15. Tromp IIM, Franco OH, van den Hooven EH, Heijboer AC, Jaddoe VWV, Duijts L, et al. 25-Hydroxyvitamin D concentrations, asthma and eczema in childhood: The generation R study. Clin Nutr 2018;37:169-76.
16. Bartley J. Vitamin D: emerging roles in infection and immunity. Expert Rev Anti Infect Ther 2010;8:1359-69.
17. Kim MJ, Kim SN, Lee YW, Choe YB, Ahn KJ. Vitamin D Status and Efficacy of Vitamin D Supplementation in Atopic Dermatitis: A Systematic Review and Meta-Analysis. Nutrients 2016;8:789.
18. Palmer DJ. Vitamin D and the Development of Atopic Eczema. J Clin Med 2015;4:1036-50.
19. Mirzakhani H, Al-Garawi A, Weiss ST, Litonjua AA. Vitamin D and the development of allergic disease: how important is it? Clin Exp Allergy 2015;45:114-25.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:365-371
DOI: 10.4274/BMJ.galenos.2023.2023.1-14

Research

Fear, Anxiety, and Obsession Levels of Dialysis Patients and Healthy Individuals During the COVID-19 Pandemic

COVID-19 Pandemisi Sırasında Diyaliz Hastaları ve Sağlıklı Bireylerin Korku, Anksiyete ve Takıntı Düzeyleri

Arife Albayrak Coşar[1], Sibel Yücel Koçak[2], Filiz Turan[3], Arzu Öztürk[3], Mürvet Yılmaz[2]

[1]Alanya Alaaddin Keykubat University Faculty of Health Science, Department of Nursing, Antalya, Türkiye
[2]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Nephrology, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Unit of Dialysis, İstanbul, Türkiye

ABSTRACT

Objective: The aim of this study was to determine the level of fear, anxiety, and obsession caused by the coronavirus disease-2019 (COVID-19) pandemic in hemodialysis (HD) and peritoneal dialysis (PD) patients, and to make a comparison with healthy individuals.

Methods: This analytical cross-sectional study was conducted with 162 people (n=162) who were HD or PD patients or healthy individuals when lockdown measures were in force. Data were collected using a personal information form, the coronavirus anxiety scale (CAS), the obsession with COVID-19 scale (OCS), and the fear of COVID-19 scale.

Results: The fear and OCS scores of the PD patients were significantly higher than those of the HD patients and healthy individuals ($p<0.01$). There was no difference between the groups with regard to the CAS scores. Positive correlations were found in the study between the COVID-19 Fear scale and the CAS and OCS ($r=0.353$; $r=0.564$ respectively; $p<0.01$). A positive correlation was also found between the COVID-19 anxiety scale and OCS ($r=0.331$; $p<0.01$).

Conclusion: The fear, anxiety, and obsession levels of HD patients were similar to those of healthy individuals, but higher in PD patients. It is recommended that doctors and nurses should provide and maintain social and psychological support in extraordinary situations such as the pandemic, especially to patients with chronic illnesses such as PD patients who have to perform their own treatment at home, in order to reduce levels of fear, anxiety, and obsession.

Keywords: Anxiety, COVID-19, fear, hemodialysis, peritoneal dialysis, obsession, healthy individual

ÖZ

Amaç: Bu çalışmanın amacı, hemodiyaliz (HD) ve periton diyalizi (PD) hastalarında koronavirüs hastalığı-2019 (COVİD-19) pandemisinin neden olduğu korku, kaygı ve takıntı düzeyini belirlemek ve sağlıklı kişilerle karşılaştırma yapmaktır.

Gereç ve Yöntem: Bu analitik-kesitsel çalışma sokağa çıkma yasağı önlemlerinin yürürlükte olduğu zamanda HD, PD hastaları ve sağlıklı bireyler olmak üzere 162 (n=162) kişi ile yapıldı. Veriler kişisel bilgi formu, COVİD-19 korku ölçeği, koronovirüs anksiyete ölçeği (CAS) ve COVİD-19 ile takıntı ölçeği (OCS) ile toplandı.

Bulgular: PD hastalarının korku ve OCS puanları HD hastaları ve sağlıklı bireylere göre anlamlı olarak daha yüksekti ($p<0,01$). CAS puanları açısından gruplar arasında fark yoktu. Çalışmada COVİD-19 korkusu ölçeğiyle, sırasıyla CAS ve OCS arasında pozitif yönlü korelasyon bulundu ($r=0,353$; $r=0,564$; $p<0,01$). COVİD-19 anksiyete ölçeğiyle OCS arasında da pozitif yönlü ilişki bulundu ($r=0,331$; $p<0,01$).

Sonuç: HD hastalarının korku, anksiyete ve obsesyon düzeyleri sağlıklı bireyler ile benzer iken PD hastalarında yüksekti. Pandemi gibi olağanüstü durumlarda özelikle tedavilerini evde kendileri sürdürmek zorunda kalan PD hastaları gibi kronik hastalığı olan hastalarda hekim ve hemşireleri tarafından korku, anksiyete ve obsesyon düzeylerinin azaltılmasına yönelik sosyal ve psikolojik desteğin sağlanması ve sürdürülmesi önerilmektedir.

Anahtar Kelimeler: Anksiyete, COVİD-19, korku, hemodiyaliz, periton diyalizi, takıntı, sağlıklı birey

Address for Correspondence: Arife Albayrak Coşar, Alanya Alaaddin Keykubat University Faculty of Health Science, Department of Nursing, Antalya, Türkiye
Phone: +90 505 806 16 62 E-mail: albayrakcosar@hotmail.com ORCID ID: orcid.org/0000-0003-3049-5895

Cite as: Albayrak Coşar A, Yücel Koçak S, Turan F, Öztürk A, Yılmaz M. Fear, Anxiety, and Obsession Levels of Dialysis Patients and Healthy Individuals During the COVID-19 Pandemic. Med J Bakirkoy 2023;19:365-371

Received: 20.01.2023
Accepted: 24.04.2023

INTRODUCTION

The coronavirus disease-2019 (COVID-19) first appeared in the city of Wuhan in China in December 2019, but spread quickly and within a short time affected the entire world. The World Health Organization declared it a pandemic on March 11, 2020 (1,2). Since its first appearance, the virus has caused the deaths of more than 6 million people (COVID-19 Visualizer, 2022 June 29). As COVID-19 continued its spread, the first case was reported in Türkiye on March 11, 2020, and from that date, measures were introduced to limit the spread of the virus, including working from home, the closure of all educational institutions, restaurants, culture and sport facilities, and public transportation systems, the restriction of travel, a lockdown, the restriction of the gathering of groups of people, and the enforcement of social distancing.

Most people who are infected with the COVID-19 show only slight or moderate symptoms that do not necessitate any particular treatment. However, in patients receiving dialysis treatment for end-stage renal disease (ESRD), there is a higher risk of serious clinical progress and a worse outcome (3). In renal failure patients who need hemodialysis (HD) or peritoneal dialysis (PD) to maintain their lives, COVID-19 increases the rate of morbidity and mortality when their immune system is under pressure because of uremia or they have more than one illness at the same time (4,5). At this time, both healthy people and the chronically ill are subjected to social isolation, separation from friends and family, and restrictions on their lives. The pandemic has increased the need for social support, especially for the chronically ill, such as those with end-stage renal failure. For this reason, cutting off social support as part of lockdown or an isolation strategy may negatively affect mental health, especially in at-risk groups, resulting in an unwillingness to accept health services, not going regularly for check-ups or going late, or developing a negative attitude toward health workers because of fear of infection (6).

The pandemic has been shown to have increased levels of fear, anxiety and obsession in the general population (7,8) and the knowledge that their risk of infection with COVID-19 is high, that they can become seriously ill, and that they may have a greater risk of death can cause greater fear, anxiety, and obsession in ESRD patients than in healthy individuals. All of these negative feelings can naturally have negative effects on mental health and on conformity to and continuation of treatment in the chronically ill (9). Accordingly, the aim of this study was to compare the levels of fear, anxiety, and obsession caused by the COVID-19 pandemic in patients receiving HD and PD treatment.

METHODS

Participants and the Procedure

This analytical cross-sectional research was conducted with healthy individuals and ESRD patients receiving treatment at the dialysis unit of a teaching and research hospital in İstanbul, Türkiye, between April 1 and 30, 2021, when lockdown measures were in force.

The study was conducted with adult (>18 years of age) patients and healthy individuals. The first and second groups comprised 50 HD patients (90.5%) and 31 PD patients (90.7%), respectively, who were regularly being followed up at the dialysis unit of a teaching and research hospital in Istanbul. The third group consisted of 81 healthy individuals who came to the hospital as friends or relatives of patients and who were contacted using a simple sampling method. Thus, 162 people were included in the study. Individuals who were aged 18 or more, had no communication impediment, had no psychiatric diagnosis, were literate, had a diagnosis of ESRD and were undergoing treatment for it, or were healthy individuals without any chronic disease were included in the research. Patients were included if they had been on regular HD (three times weekly, four hours per session) or PD (continuous ambulatory PD or automated PD) for at least three months. The data collection instruments were handed out to the participants and then collected after completion. Completing the data collection instruments took approximately 10-15 minutes.

The patients and healthy individuals were informed about the study, and signed informed consent forms were obtained according to the Helsinki Declaration before they were included in the study. Before starting the research, approval was obtained from the Ministry of Health (2021-02-07T14_34_35) and from the Ethics Committee of Alanya Alaaddin Keykubat University Faculty of Medicine Clinical Research Ethics Committee (decision no: 05-05, date: 10.03.2021). Institutional permission was obtained from the hospital where the research was conducted.

Measures

Data collection was achieved using a personal information form, created by the researchers after a scan of the literature and consisting of 16 questions on sociodemographic characteristics and HD and PD patients' clinical parameters (4,10-12), the coronavirus anxiety scale (CAS), the obsession with COVID-19 scale (OCS), and the fear of COVID-19 scale (FCV-19S) (13-15).

The FCV-19S was developed to measure the levels of fear arising from COVID-19. The scale has a single dimension and

seven items of five-way Likert type (1= I definitely disagree, 5= I definitely agree). Item-total correlations were between 0.47 and 0.56, and factor loads varied 0.66 and 0.74. Internal consistency was high (α=0.80), and test-retest reliability was at an acceptable level (r=0.72). A higher score on the scale indicates a higher level of fear related to COVID-19 (13). The Turkish version of the scale has powerful psychometric characteristics (11). In this study, the Cronbach's alpha was 0.87.

The OCS measures an individual's experience of persistent and disturbing thoughts related to COVID-19 over the previous two weeks. It is a four-item self-reporting instrument in which each item is evaluated on a five-point scale from 0 (not at all) to 4 (almost every day). The score range is 0-16, and higher scores indicate a higher rate of obsessive thought. A score of 7 or more indicates a problematic or dysfunctional thought. It is a reliable (α>0.83) and valid instrument (14). The Turkish version of the scale was used (10). In our study, the Cronbach's alpha was found to be 0.600.

The CAS is a five-item scale scored between 0 (not at all) and 5 (almost every day). Measures an individual's experience of anxiety related to COVID-19 over the previous two weeks. The score is between 0 and 20, and the cutoff score is 9. High scores are considered problematic. The internal consistency of the scale was high (α=0.93). The scale has high diagnostic characteristics, with 90% sensitivity and 85% specificity (15). The Turkish version used has powerful psychometric characteristics (10). Cronbach's alpha in our study was 0.828.

Statistical Analysis

The program Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) was used for the statistical analyses, and descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used in the evaluation of the study data. The conformity of quantitative data to normal distribution was tested using the Shapiro-Wilk test and graphical examinations. In comparisons of quantitative data that showed normal distribution between more than two groups, one-way variance analysis and Bonferroni two-way evaluations were used. In comparisons of quantitative data that did not show normal distribution between more than two groups, the Kruskal-Wallis test and the Dunn-Bonferroni test were used. The Pearson chi-square test and Fisher-Freeman-Halton exact test were used for the comparison of qualitative data. The Spearman correlation test was used to evaluate correlations between quantitative variables. Statistical significance was taken as p<0.05.

RESULTS

Table 1 shows the sociodemographic data of the participants. As a whole and as groups, the distributions of the participants were similar in terms of gender, marital status, education status, and economic status (p>0.05). The mean age of individuals included in the study was 48.14±14.52, and there was no statistically significant difference in the mean ages of the PD and HD patients. The mean age of the healthy individuals was found to be significantly lower than that of the HD and PD patients (p<0.01). No statistically significant difference was found between the groups of participants according to whether they had had COVID-19, whether they received support from their families, or whether family members had had COVID-19 (p>0.05). All HD patients received HD treatment three times a week, and the primary diagnosis of 50% was hypertension. The HD patients had been on dialysis for a mean of 64.90±42.47 months. Examining the clinical characteristics of the PD patients, it was observed that the type of dialysis of 58.1% was continuous ambulatory PD. The primary diagnosis was 38.7% hypertension, and they had been receiving treatment for a mean of 50.65±32.19 months.

Table 2 shows the participants' mean FCV-19S, CAS, and OCS scores. The mean score obtained from the participants on the FCV-19S was 17.85±6.21, and there was a statistically significant difference between the groups (p<0.01). According to two-way comparisons to determine the difference, the mean scores of PD patients on the FCV-19S were higher than those of healthy individuals and HD patients (p<0.01).

The total mean score on the CAS was 1.09±2.5, and there was no statistically significant difference between the groups (p>0.05).

The participants' mean score on the OCS was 3.35±2.26, and a statistically significant difference was found between the groups (p<0.01). According to two-way comparisons, the scores obtained by PD patients on the OCS were significantly higher than those of healthy individuals or HD patients (p<0.05).

Table 3 shows the correlation between fear of COVID-19, CAS, and OCS scores. A weak positive correlation was found between the total mean score on the FCV-19S and CAS (r=0.353; p<0.01). A medium-level positive correlation was found between the total mean score on the FCV-19S and OCS (r=0.564; p<0.01). A weak but statistically significant positive correlation was found between the mean CAS score and the mean total OCS score (r=0.331; p<0.01).

Table 1. Demographic, clinical and sociocultural data of the participants

		All (n=162) n (%)	HD (n=50) n (%)	PD (n=31) n (%)	Healthy individual (n=81)	p-value
Mean age (years); mean ± SD		48.14±14.52	54.20±16.01	51.19±11.80	43.23±12.82	[a]**0.001****
Sex	Female	87 (53.7)	22 (44)	19 (61.3)	46 (56.8)	[c]0.232
	Male	75 (46.3)	28 (56)	12 (38.7)	35 (43.2	
Primary kidney disease	Hypertension		25 (50)	12 (38.7)		
	Diabetes mellitus		13 (26)	4 (12.9)		
	Glomerulonephritis		7 (14)	3 (9.7)		
	Cystic kidney disease		1 (2)	2 (6.5)		
	Other/unknown		4 (8)	10 (32.3)		
Dialysis vintage (months); median (min-max) Mean ± SD			60 (6-156) 64.90±42.47	52 (6-126) 50.65±32.19		
Marital status	Married	107 (66.0)	30 (60.0)	24 (77.4)	53 (65.4)	[c]0.270
Education	Literate	28 (17.3)	11 (22.0)	7 (22.6)	10 (12.3)	[b]0.203
	Primary/secondary school	83 (51.2)	29 (58.0)	14 (45.2)	40 (49.4)	
	High school	44 (27.2)	8 (16.0)	10 (32.3)	26 (32.1)	
	University or higher	7 (4.3)	2 (4.0)	0 (0.0)	5 (6.2)	
Economical status	Income less than expenses	68 (42.0)	26 (52.0)	12 (38.7)	30 (37.0)	[c]0.150
	Income equals expense	75 (46.3)	19 (38.0)	18 (58.1)	38 (46.9)	
	Income more than expenses	19 (11.7)	5 (10.0)	1 (3.2)	13 (16.0)	
Family member support	Anytime	96 (59.3)	33 (66.0)	22 (71.0)	41 (50.6)	[c]0.143
	Never	32 (19.8)	9 (18.0)	6 (19.4)	17 (21.0)	
	Sometime	34 (21.0)	8 (16.0)	3 (9.7)	23 (28.4)	
COVID-19 diagnosis		40 (24.7)	14 (28.0)	9 (29.0)	17 (21.0)	[c]0.547
COVID status of family members		45 (27.8)	8 (16.0)	11 (35.5)	26 (32.1)	[c]0.077
Type of kidney replacement therapy	**HD** Three per week		50 (100)			
	PD CAPD			18 (58.1)		
	APD			13 (41.9)		

HD: Hemodialysis, PD: Peritoneal dialysis, CAPD: Continuous ambulatory peritoneal dialysis, APD: Automated peritoneal dialysis, COVID-19: Coronavirus disease-2019, SD: Standard deviation, min-max: Minimum-maximum
[a]One-Way ANOVA, [b]Fisher-Freeman-Halton test, [c]Pearson chi-square test, **p<0.01, significant p-values are written in bold

Table 2. FCV-19S, CAS, and OCS scores of participants by total and groups

	All (n=162)	HD (n=50)	PD (n=31)	Healthy individual (n=81)	p-value
FCV-19S score: mean ± SD	17.85±6.21	16.76±5.29	24.35±4.67	16.02±5.64	[d]**0.001****
Median (min-max)	18 (7-31)	17 (7-29)	25 (12-31)	16 (7-26)	
CAS score: mean ± SD	1.09±2.5	1.22±2.44	1.9±3.92	0.7±1.66	[d]0.206
Median (min-max)	0 (0-16)	0 (0-10)	0 (0-16)	0 (0-10)	
OCS score: mean ± SD	3.35±2.26	3.4±1.88	4.97±2.01	2.7±2.26	[d]**0.001****
Median (min-max)	3 (0-10)	3 (0-7)	5 (2-10)	2 (0-10)	

FCV-19S: Fear of COVID-19 scale, CAS: Coronavirus anxiety scale, OCS: Obsession with COVID-19 scale, COVID-19: Coronavirus disease-2019, HD: Hemodialysis, PD: Peritoneal dialysis, SD: Standard deviation, min-max: Minimum-maximum , [d]Kruskal Wallis Test, **p<0.01

Table 3. The relationship between FCV-19S, CAS, and OCS scales

	CAS		OCS	
	r	p	r	p
FCV-19S	0.353†	**0.001****	0.564†	**0.001****
CAS	-	-	0.331†	**0.001****

†r= Spearman correlation coefficient, **p<0.01. Significant p-values are written in bold.
CAS: Coronavirus anxiety scale, FCV-19S: Fear of COVID-19 scale, OCS: Obsession with COVID-19 scale, COVID-19: Coronavirus disease-2019

DISCUSSION

Our study is the first to compare the state of fear, obsession, and anxiety in HD and PD patients and healthy individuals in the COVID-19 pandemic. It was found in our study that the pandemic caused fear, anxiety and obsession in all individuals, whether or not they had a chronic illness, and that fear, anxiety and obsession were greater in PD patients than in HD patients and healthy individuals. The mean ages of HD and PD patients in our study were similar, and the mean age of healthy individuals was significantly lower. The HD, PD, and healthy groups were similar in terms of gender, economic status, and educational status. There was no significant difference between the groups of participants about support by family members, having had COVID-19, or having a family member who had had COVID-19.

In its early stages, the outbreak of COVID-19 caused worldwide fear, anxiety, and uncertainty. Uncertainty and feelings such as fear, unhappiness, and helplessness felt because of worry about the disease caused intense stress (9). In our study also, the participants' fear of COVID-19 was found to be at a medium level. It was also found in a comparison between the groups that the fear of COVID-19 in PD patients was significantly greater than that in HD patients or healthy individuals. In a meta-analysis by Luo et al. (8), it was determined that fear of COVID-19 was high worldwide. In a study by Bakioğlu et al. (16), the fear of COVID-19 in chronically ill individuals was greater than in individuals who were not chronically ill. Haktanir et al. (17) reported that no significant difference was found between healthy individuals and those who were chronically ill. It was found in our study that there was no significant difference in levels of fear between HD patients and healthy individuals included in the study. This result is similar to that of Haktanir et al. (17). However, in our study, the fear levels of the PD patients were found to be greater than those of the healthy individuals, and this result is similar to the study by Bakioğlu et al. (16,17). All clinics in hospitals were set aside for COVID-19 treatment, but HD units continued to accept and treat patients. It is thought that the fear levels of PD patients were higher because PD patients had to manage their own treatment at home, hospitals did not accept patients other than in an emergency, all clinics were set aside for COVID-19 treatment, intensive care units were full of COVID-19 patients, social support was reduced because of the lockdowns, and all sources of information during the pandemic emphasized that COVID-19 had a greater effect on those with chronic health problems.

Anxiety plays an important role in our ability to continue our lives, but when it is at a high level, it prevents us from acting and continuing our daily lives and can sometimes even put us in danger (18). This study was conducted using people who were particularly sensitive to COVID-19 infection, and their general anxiety was found to be 44.7% (19). In a study by Hyland et al. (20), it was found that two out of four (27.7%) people who were in quarantine for COVID-19 had general anxiety disorder and depression. The mean score obtained from the participants in our study on the CAS was below the cutoff point, and no significant difference was found between the groups. Recently, in a study by Karaca et al. (12) comparing the psychological state of HD and PD patients in the period of social isolation because of COVID-19, it was reported that the scores obtained by PD patients on the hospital anxiety and depression scale were higher than those of HD patients, although the difference was not significant. In our study, the scores obtained on the COVID-19 anxiety scale by PD patients were higher than those of HD patients and healthy individuals, although this difference was not significant. It is thought that the high fear levels of patients with PD increased their levels of anxiety.

COVID-19 is a fast-spreading disease, and for this reason, measures were taken at a national and global level so that it would not affect the broader population. These measures included staying at home, regular hand washing, keeping a distance of at least 1 meter between people, using masks, washing produce brought into the house, and ventilation. Continuing the use of these measures for a long time causes obsessive behavior in people (21-23). In our study, it was found that the scores of PD patients on the obsession scale were significantly higher than those of HD patients or healthy individuals. In a study by Abba-Aji et al. (22) with 6041 people in the early period of the pandemic, it was reported that the prevalence of symptoms of obsessive-compulsive disorder was higher than before the pandemic. In our study, it was found that obsession levels were high in PD patients but low in HD patients and healthy individuals (22). This is because PD patients are far away from a dialysis center and manage all their treatment for themselves at home;

they perform their own dialysis; they pay more attention to measures such as regular hand washing, hygiene, and the use of face masks and gloves to avoid infection with the virus; and they regularly see news of COVID-19-related deaths on the media, which puts them into a state of obsession, so that their obsession levels may rise. It is thought that the low levels of obsession in the HD patients compared with the PD patients in our study arises from the high level of protective measures in HD units – drawing curtains between patients, not entering the unit without a mask, wearing a mask throughout the session, restricting entry and exit, and use of personal protective equipment by the staff – and from the provision of a fault-free service. During their treatment, HD patients can establish face-to-face communication with the health team, they can ask the doctors and nurses questions about COVID-19 face to face, they can share their concerns and worries, and they can communicate with other patients, socialize, and share their feelings, which may reduce their fear, anxiety, and obsessions.

The lack of confidence, fear of uncertainty, and strict measures taken have awakened a strong emotional reaction in the general population, which may lead to psychological problems. It was found in our study that emotional reactions such as fear, anxiety, and obsession, which could cause psychological problems, were felt particularly in the PD group, who had to manage their treatment at home by themselves and who were socially isolated to a greater extent than the HD group or healthy individuals.

CONCLUSION

It was found in our study that the levels of fear, anxiety, and obsession of HD patients were similar to those of healthy individuals, but in PD patients they were higher. It is recommended that in extraordinary situations such as the pandemic, doctors and nurses should provide and maintain social and psychological support to lower levels of fear, anxiety, and obsession in the chronically ill, such as PD patients who are obliged to carry on their treatment by themselves at home.

Acknowledgments: We thank Emire Bor, EMPIAR Statistics, for performing statistical analysis of the study. The present authors are especially grateful to all dialysis patients and healthy individuals who participated in this study.

ETHICS

Ethics Committee Approval: Before commencing the research, approval was obtained from the Ministry of Health (2021-02-07T14_34_35) and from the Clinical Research Ethics Committee of Alanya Alaaddin Keykubat University Faculty of Medicine (decision no: 05-05, date: 10.03.2021). Institutional permission was obtained from the hospital where the research was conducted.

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

Authorship Contributions

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

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. WHO. World Healt Organisation. Coronavirus [Internet]. [cited 2020 Feb 6]. Available from: https://www.who.int/health-topics/coronovirüs
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
3. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430-6.
4. Kocak SY, Kayalar AO, Karaosmanoglu HK, Yilmaz M. COVID-19 in hemodialysis patients: a single-center experience in Istanbul. Int Urol Nephrol 2021;53:2385-97.
5. Jager KJ, Kramer A, Chesnaye NC, Couchoud C, Sánchez-Álvarez JE, Garneata L, et al. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. Kidney Int 2020;98:1540-8.
6. Hawryluck L, Gold WL, Robinson S, Pogorski S, Galea S, Styra R. SARS control and psychological effects of quarantine, Toronto, Canada. Emerg Infect Dis 2004;10:1206-12.
7. Ozamiz-Etxebarria N, Dosil-Santamaria M, Picaza-Gorrochategui M, Idoiaga-Mondragon N. Stress, anxiety, and depression levels in the initial stage of the COVID-19 outbreak in a population sample in the northern Spain. Cad Saude Publica 2020;36:e00054020.
8. Luo F, Ghanei Gheshlagh R, Dalvand S, Saedmoucheshi S, Li Q. Systematic Review and Meta-Analysis of Fear of COVID-19. Front Psychol 2021;12:661078.
9. Xiao H, Zhang Y, Kong D, Li S, Yang N. Social Capital and Sleep Quality in Individuals Who Self-Isolated for 14 Days During the Coronavirus Disease 2019 (COVID-19) Outbreak in January 2020 in China. Med Sci Monit 2020;26:e923921.
10. Evren C, Evren B, Dalbudak E, Topcu M, Kutlu N. Measuring anxiety related to COVID-19: A Turkish validation study of the Coronavirus Anxiety Scale. Death Stud 2022;46:1052-8.
11. Satici B, Gocet-Tekin E, Deniz ME, Satici SA. Adaptation of the Fear of COVID-19 Scale: Its Association with Psychological Distress and Life Satisfaction in Turkey. Int J Ment Health Addict 2021;19:1980-8.
12. Karaca C, Eren N, Dincer MT, Turan S, Karaca HK, Kucuk M, et al. How Dialysis Patients Cope with a Curfew? A Comparison of Psychological Status between Hemodialysis and Peritoneal Dialysis Patients During the COVID-19 Pandemic. Blood Purif 2022;51:458-63.

13. Ahorsu DK, Lin CY, Imani V, Saffari M, Griffiths MD, Pakpour AH. The Fear of COVID-19 Scale: Development and Initial Validation. Int J Ment Health Addict 2020;20:1537-45.
14. Lee SA. How much "Thinking" about COVID-19 is clinically dysfunctional? Brain Behav Immun 2020;87:97-8.
15. Lee SA. Coronavirus Anxiety Scale: A brief mental health screener for COVID-19 related anxiety. Death Stud 2020;44:393-401.
16. Bakioğlu F, Korkmaz O, Ercan H. Fear of COVID-19 and Positivity: Mediating Role of Intolerance of Uncertainty, Depression, Anxiety, and Stress. Int J Ment Health Addict 2021;19:2369-82.
17. Haktanir A, Seki T, Dilmaç B. Adaptation and evaluation of Turkish version of the fear of COVID-19 Scale. Death Stud 2022;46:719-27.
18. Koçak Z, Harmancı H. Mental Health in the Family During the COVID-19 Pandemic Process. Journal of Karatay Social Research 2020;5:183-207.
19. Liu S, Yang L, Zhang C, Xiang YT, Liu Z, Hu S, et al. Online mental health services in China during the COVID-19 outbreak. Lancet Psychiatry 2020;7:17-8.
20. Hyland P, Shevlin M, McBride O, Murphy J, Karatzias T, Bentall RP, et al. Anxiety and depression in the Republic of Ireland during the COVID-19 pandemic. Acta Psychiatr Scand 2020;142:249-56.
21. Özçakmak S, Var I. Good Hygiene Practices to Prevent Covid-19 Outbreak Spreading. Akademik Gıda 2020;18:433-41.
22. Abba-Aji A, Li D, Hrabok M, Shalaby R, Gusnowski A, Vuong W, et al. COVID-19 pandemic and mental health: Prevalence and correlates of new-onset obsessive-compulsive symptoms in a Canadian province. Int J Environ Res Public Health 2020;17:6986.
23. Erkal E, Ses A, Aydın S, Çalışkan D. Non-Pharmaceutical Public Health Measures to Prevent the Transmission of COVID-19 in Community. ESTUDAM Public Health Journal 2020;5:79-95.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:372-381
DOI: 10.4274/BMJ.galenos.2023.2023.3-14

Research

Effect of Mutational Difference on Systemic Immune Inflammation Index in Patients with a Diagnosis of COVID-19

COVİD-19 Tanılı Hastalarda Mutasyon Farklılığının Sistemik İmmün Enflamasyon İndeksi Üzerine Etkisi

Deniz Yılmaz[1], Felemez Arslan[1], Ezgi Şahin[1], Betül Erişmiş[1], Faruk Karandere[1], İnci Öztel[1], Yusuf Emre Özdemir[2], Habip Gedik[2], Mehmet Hurşitoğlu[1]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Türkiye

ABSTRACT

Objective: Mutations in coronavirus 2 [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] are a considerable issue. It could affect the infectivity and outcome of coronavirus disease-2019 (COVID-19) infection. In this prospective study, we compared the characteristics and outcomes of the main SARS-CoV-2 variants in our non-intensive care unit pandemic service inpatients.

Methods: In this study, 2,090 COVID-19 inpatients were included. The numbers of patients with alpha (group 1), delta (group 2), and omicron (group 3) variants were 701, 699, and 690, respectively.

Results: The median age of group 3 patients was significantly higher than that of the others, and the female/male ratio and presence of diabetes mellitus of group 1 patients were significantly lower than those of the others ($p<0.05$, both). Regarding the hospital stay period and outcome, group 1 patients had the highest mortality rate ($p<0.05$, Eta square =0.12). Regression analysis showed that the presence of the alpha variant, severe chest computed tomography findings and chronic kidney disease, long hospital stay, and high serum C-reactive protein and D-dimer levels at admission were risk factors for a poor outcome.

Conclusion: Early admission and/or easily obtainable clinical and laboratory determinant parameters of poor outcome could be a pathfinder for clinicians and/or researchers dealing with this challenging contagious viral disease.

Keywords: SARS-CoV-2, alpha, delta, omicron, COVID-19

ÖZ

Amaç: Koronavirüs 2'deki mutasyonlar [şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2)] önemli bir sorundur. Bulaşıcılığı ve koronavirüs hastalığı-2019 (COVİD-19) enfeksiyonunun sonucunu etkileyebilir. Bu prospektif çalışmada, yoğun bakım ünitesi dışı pandemi servislerinde yatan hastaların ana SARS-CoV-2 varyantlarının özellikleri ve sonuçları karşılaştırmaya çalışıldı.

Gereç ve Yöntem: Bu çalışmaya toplam 2.090 COVİD-19 tanısı ile yatan hasta dahil edildi. Alfa (grup 1), delta (grup 2) ve omicron (grup 3) varyant hasta sayısı sırasıyla 701, 699 ve 690 idi.

Bulgular: Grup 3 hastalarının ortanca yaşı diğerlerinden anlamlı olarak yüksekti ve grup 1 hastalarının kadın/erkek oranı ve diabetes mellitus varlığı diğerlerinden anlamlı derecede düşüktü ($p<0,05$, her ikisi de). Hastanede yatış süresi ve yatış komplikasyonu ile ilgili olarak, grup 1'deki hastalar en yüksek mortalite oranına sahipti ($p<0,05$, Eta kare =0,12). Regresyon analizi; alfa varyantı varlığının, şiddetli toraks bilgisayarlı tomografi bulgularının, kronik böbrek hastalığının, hastanede uzun yatış süresinin, başvuru sırasındaki yüksek serum C-reaktif protein ve D-dimerinin morbidite ve mortalite için risk faktörleri olduğunu gösterdi.

Sonuç: Bu erken dönemdeki yatış ve/veya komplikasyon sonucunun pratik olarak elde edilebilen klinik ve laboratuvar belirleyici parametreleri, bu tür zorlu bulaşıcı viral hastalıklarla ilgilenen klinisyen ve/veya araştırmacılar için yol gösterici olabilir.

Anahtar Kelimeler: SARS-CoV-2, alpha, delta, omicron, COVİD-19

Address for Correspondence: Felemez Arslan, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
Phone: +90 543 835 57 97 E-mail: feloarslan@gmail.com ORCID ID: orcid.org/0000-0001-8318-1860

Cite as: Yılmaz D, Arslan F, Şahin E, Erişmiş B, Karandere F, Öztel İ, Özdemir YE, Gedik H, Hurşitoğlu M. Effect of Mutational Difference on Systemic Immune Inflammation Index in Patients with a Diagnosis of COVID-19. Med J Bakirkoy 2023;19:372-381

Received: 25.03.2023
Accepted: 25.06.2023

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a highly contagious viral infection (1). Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) demonstrates a somewhat lower mutational rate than other RNA viruses, approximately 12,800 mutations have been identified (2). The well-known variants are alpha B.1.1.7 (known as 20I/501Y.V1, VOC 202012/01), beta B.1.351 (known as 501Y.V2), and gamma P.1 (known as alpha, delta, and omicron) are the main determining responsible variants for COVID-19 infection in Türkiye World Health Organization (3). The last VOC of the SARS-CoV-2 virus is the omicron (4). Alpha, delta, and omicron are the main determining variants responsible for COVID-19 infection in Türkiye (5). As mentioned in a study by Loucera et al. (6), combining genomic data with patients' clinical data will help us better understand the effect of mutations on the outcome of this challenging infection. To the best of our knowledge (at least in Türkiye), there are no studies assessing patients' early admission clinical, laboratory, and radiological characteristics according to the variants of SARS-CoV-2 viruses. In this retrospective study, we attempted to study these issues in our hospital's non-critical alpha, delta, and omicron variants infected by COVID-19 in-patients.

METHODS

This retrospective study was approved by University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital's Clinical Research Ethics Committee (decision no: 2022-12-18, date: 20.06.2022). Data of the above-mentioned hospital's medical pandemic services for COVID-19 patients were collected. According to the dates of predominance of alpha (01 April-30 June 2021), delta (01 August-30 November 2021), and omicron (01 January-30 April 2022) variants, COVID-19 patients were divided into group 1 (alpha), group 2 (delta), and group 3 (omicron), respectively.

Inclusion criteria;

1. Age >18 years old,

2. Positivity of the COVID-19 real-time reverse transcriptase polymerase chain reaction test at admission,

3. Presence of first-day admission laboratory records.

Exclusion criteria;

1. Those who were discharged at their request before completing their treatment and follow-up,

2. Taking medications that could affect routine laboratory measures (such as steroids, chemotherapy, radiotherapy, etc.) (within one month of the diagnosis of COVID-19 infection).

Behind demographic, clinical characteristics, and the outcome of the patients, their early admission laboratory and radiology investigations were recorded. In addition, comorbidities [such as hypertension (HT), diabetes mellitus (DM), ischemic heart disease, etc.] were recorded. Chronic kidney disease (CKD) stage ≥2 was also included in the analysis (7).

Chest computed tomography (CT) scoring system;

The semiquantitative CT severity scoring system was used (8). The scoring system was as follows: 0= no involvement, 1= less than 5% involvement, 2=5-25% involvement, 3=26-50% involvement, 4=51-75% involvement, and 5 more than 75% involvement. The sum of these yields a total score ranging from 0 to 25 points. A score of 0-8 is accepted as mild, 9-16 as moderate, and ≥17 as severe lung involvement.

Systemic immune-inflammation index;

This blood parameter was calculated using the formula: neutrophil × platelet (PLT)/lymphocyte (9).

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 statistical package for Windows. Our study parameters data showed a non-normal distribution. Therefore, the description of data was expressed by median and interquartile range. For categorical measures, ratios and/or percentages were used. For the comparison of the 2 groups, the Mann-Whitney U test was used. Otherwise, the Kruskal-Wallis test was used for the comparison of ≥3 groups parameters. The Games Howell test was used as a post-hoc test of the Kruskal-Wallis test. The effect size (ES) was determined using Eta square ($\eta 2$) or epsilon square ($\epsilon 2$) tests, as appropriate. The values of these tests range between 0 (no association) and 1 (complete association) (1). A comparison of frequencies was performed by the chi-square test. For the degree of association, a Cramer's V value was determined (between 0.0-1.0). A Cramer's V value close to 0.00 indicates no association. A value >0.15 indicates a strong association, and >0.25 indicates a strong association (10). Spearman tests were also used to evaluate the correlation between quantitative variables. Regression analysis was performed by putting the presence or absence of the nominal. Also by putting laboratory parameters (median value) into 2 different logistic regression models (Model: Forward LR) (adjusting od ratio at 95% confidence interval). A p-value <0.05 was accepted as significant for all others.

Informed consent was obtained from each subject before the study. We are committed to protecting patient privacy and complying with the Declaration of Helsinki.

RESULTS

The final analysis was performed with 2,090 patients. The female/male ratio and median (minimum-maximum) age of them were 938 (44.90%)/1152 (55.10%), and 63.00 (18.00-97.00) years old, respectively. The numbers of alpha, delta, and omicron variants were 701, 699, and 690, respectively. A comparison of the study parameters between alpha (group 1), delta (group 2), and omicron (group 3) mutant patients is shown in Table 1. As seen in this table, the median age of group 3 patients was significantly higher than that of the other 2 groups ($p<0.05$, both, and ES =0.53). On the other hand, the female/male ratio and presence of DM in group 1 patients were significantly lower than those in groups 2 and 3 ($p<0.05$, all, and ES was 0.10, and 0.36, respectively). In addition, group 2 patients had a significantly lower rate of HT and cardiovascular disease (CVD) than the other 2 groups ($p<0.05$, all, and ES was 0.10, and 0.09, respectively). The CKD rate of group patients was higher than that of the other two groups ($p<0.05$, and ES =0.11). Although the rate of patients with no comorbidities was lowest in group 1, the rate of patients with 1, 2, and ≥3 comorbidities was significantly lower in group 2 ($p<0.05$, all, and ES =0.35). Regarding the hospital stay period and outcome, group 1 patients had the longest hospital stay and highest mortality rate than the other two groups ($p<0.05$, both, and ES was 0.81, and 0.12, respectively).

A comparison of the study parameters of our study of COVID-19 patients (n=2,090) according to the outcome of survival (n=1,704) or death (n=386) is shown in Table 2. Table 2 presents a comparison of the study parameters for our study of COVID-19 patients. The total number of patients in the study was 2,090, out of which 1,704 survived and 386 unfortunately passed away. Those who died were significantly older than those who survived this infection ($p<0.05$, ES =1.99). The ratio of the F/M ratio of the dead patients was lower than that of the survived patients (154/232 versus 784/920, respectively, $p<0.05$ and EF =0.047). Regarding the comorbidities, the presence rates of HT, CKD, and CVD in the dead group were higher than those in the survived group ($p<0.05$, all, and ES was 0.056, 0.069, and 0.074, respectively). On the other hand, the rate of the presence of DM was higher in the surviving group but not reached a statistical significance ($p>0.05$). Comparison according to the number of comorbidities showed a non-significant difference between the surviving and dead patient groups ($p>0.05$). The presence of severe chest CT findings at admission and hospital stay period of the dead patients was higher than the survived patients, while the early admission $\%SO_2$ levels showed an opposite pattern ($p<0.05$, all, and ES was 0.233 and 0383, 0.389, respectively). Regarding the early admission laboratory blood tests measure, the median Hgb level eosinophils, lymphocytes, and PLT counts were significantly higher in the survived, and the median remaining blood test levels were significantly higher in the dead patients' group (for the details see Table 2). Table 2 provides detailed information about the study parameters in relation to the outcome of survival or death among COVID-19 patients. The results indicate that the presence of severe chest CT findings upon admission and the duration of hospital stay were more frequent in patients who did not survive compared with those who survived ($p<0.05$). Conversely, the levels of early admission $\%SO_2$ (oxygen saturation) showed the opposite trend, being higher in the survival group ($p<0.05$). The ES for these associations were 0.233 and 0.38. Regarding the early admission laboratory blood tests, the median levels of hemoglobin (Hgb), eosinophils, lymphocytes, and PLT counts were significantly higher in the group of patients who survived, whereas the median levels of the remaining blood tests were significantly higher in the group of patients who died. Further details can be found in Table 2.

The regression analysis of parameters that could affect the outcome is shown in Table 3. The mortality risk is 1.94 times higher in patients with alpha variants. There is a 1.25-fold mortality risk in the delta, but it was not significant ($p>0.05$); 1.70 times in those with severe chest CT finding, 2.70 times in the presence of CKD, 1.02 times in mortality risk with one unit increase in length of stay, 0.92 times in mortality when income saturation increases by one unit, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer increases by n units mortality risk increases by 1,002, 1,006, 1.04, respectively. Table 3 displays the results of the regression analysis conducted to examine the parameters that could impact the outcome. The findings reveal that individuals with alpha variants of COVID-19 have a 1.94 times higher risk of mortality. Similarly, there was a 1.25-fold mortality risk associated with the delta variant, although this finding did not reach statistical significance ($p>0.05$). Moreover, the presence of severe chest CT findings was linked to a 1.70-fold higher mortality risk. Patients with CKD face a significantly elevated mortality risk of 2.70 times. Additionally, for every unit increase in the length of hospital stay, there is a 1.02 times higher mortality risk. Conversely, a one-unit increase in oxygen saturation levels leads to a mortality risk of 0.92 times. Furthermore, the mortality risk

Table 1. Comparison of study parameters according to mutations

	Mutation				
Parameter	**Alpha1 n=701**	**Delta2 n=699**	**Omicron3 n=690**	**p-value**	**Effect size**
Gender				**<0.001**	0.10[a]
Female	261 (37.2%)	330 (47.2%)	347 (50.3%)		
Male	440 (62.8%)	369 (52.8%)	343 (49.7%)		
Post-hoc		1-2, 1-3			
Age (years)				**<0.001**	0.053[b]
Median	62.50	63.00	70.00		
IQR	16.00	28.00	22.00		
Q1-Q3	53.00-70.00	48.00-76.00	59.00-81.00		
Range	18.00-97.00	18.00-95.00	20.00-97.00		
Post-hoc		1-3, 2-3			
Hypertension				**<0.001**	
Absent	330 (47.1%)	394 (56.4%)	309 (44.8%)		0.10[a]
Present	371 (52.9%)	305 (43.6%)	381 (55.2%)		
Post-hoc		2-1, 2-3			
Diabetes mellitus				**<0.001**	
Absent	226 (32.2%)	506 (72.4%)	473 (68.7%)		0.36[a]
Present	475 (67.8%)	193 (27.6%)	216 (31.3%)		
Post-hoc		1-2, 1-3			
Chronic kidney disease				**<0.001**	0.11[a]
Absent	658 (93.9%)	651 (93.1%)	601 (87.1%)		
Present	43 (6.1%)	48 (6.9%)	89 (12.9%)		
Post-hoc		3-1, 3-2			
Cardiovascular disease				**<0.001**	0.09[a]
Absent	539 (76.9%)	581 (83.1%)	512 (74.2%)		
Present	162 (23.1%)	118 (16.9%)	178 (25.8%)		
Post-hoc		2-1, 2-3			
Numbers of comorbidities				**<0.001**	0.35[a]
0	119 (17.0%)	307 (43.9%)	172 (24.9%)		
1	217 (31.0%)	146 (20.9%)	163 (23.6%)		
2	200 (28.5%)	138 (19.7%)	196 (28.5%)		
≥3	165 (23.5%)	108 (15.5%)	159 (23.0%)		
Post-hoc		1-2, 1-3, 2-3			
Chest CT findings				**<0.001**	0.32[a]
Not severe	457 (65.3%)	590 (89.5%)	596 (92.7%)		
Severe	243 (34.7%)	69 (10.5%)	47 (7.3%)		
Mortality				**<0.001**	0.12[a]
Survived	526 (75.0%)	583 (83.4%)	595 (86.2%)		

Table 1. Continued					
Died	175 (25.0%)	116 (16.6%)	95 (13.8%)		
Post-hoc		1-2, 1-3			
Duration of hospital stay (days)				**<0.001**	0.081[b]
Median	14.00	9.00	9.00		
IQR	11.00	8.00	9.00		
Q1-Q3	14.00-20.75	6.00-14.00	6.00-15.00		
Range	0.00-104.00	4.00-85.00	1.00-128.00		
Post-hoc		1-2, 1-3			
SII (x10^9 cells/L)				**<0.001**	0.013[b]
Median	957.00	1043.80	1368.99		
IQR	1553.36	1545.16	2202.98		
Q1-Q3	513.95-2067.30	539,91-2085,07	676.91-2879.89		
Range	4.33-720438.09	25.76-17818.18	0.00-22016.94		
Post-hoc	2-3				
Platelet count (x10^9 cells/L)				**<0.001**	0.014[b]
Median	199.00	192.00	218.50		
IQR	101.50	101.00	117.25		
Q1-Q3	154.00-255.50	152.00-253.00	166.00-283.25		
Range	9.00-954.00	26.00-803.00	8.00-1147.00		
Post-hoc	3-1, 3-2				
Lymphocyte count (x10^9 cells/L)				**<0.001**	0.008[b]
Median	1060.00	930.00	1040.00		
IQR	830.00	750.00	950.00		
Q1-Q3	710.00-1540.00	600.00-1350.00	660.00-1610.00		
Range	2.10-1175.00	70.00-18340.00	40.00-144810.00		
Post-hoc	1-2				
Neutrophil count (x10^9 cells/L)				**<0.001**	0.021[b]
Median	5150.00	5200.00	6670.00		
IQR	4200.00	4230.00	5562.50		
Q1-Q3	3700.00-7900.00			3520.00-7750.00	4152.50-9715.00
Range	40.00-18700.00	126.00-19720.00	0.00-30620.00		
Post-hoc	3-1, 3-2				

IQR: Interquartile range, CT: Computed tomography, SII: Systemic immune-inflammation index
Kruskal-Wallis test, Post-hoc: Games Howell test, statistically significant p<0.05.
[a]Eta square [(**η**2), [b]Epsilon sqare (**ϵ**2) (degree of freedom =2)].

increased by 1,002, 1,006, and 1.04 times with each unit increase in LDH, CRP, and D-dimer levels, respectively. These results provide important insights into the various factors that can influence mortality outcomes.

DISCUSSION

In our study, the ratio of female/male in Alpha variant-infected COVID-19 inpatients was significantly lower than the ratio of the other two variant-infected patient groups. On the other hand, the median age of the omicron variant

Table 2. Comparison of study parameters according to outcomes

	Outcome				
Parameters	**Survived (n=1704)**	**Died (n=386)**	**df**	**p**	**Effect size**
Age (years)			**1**	**<0.001**	0.199
Median	64.00	70.00			
IQR	23.00	19.00			
Range	18.00-96.00	25.00-97.00			
Gender			**1**	**0.029**	0.047[a]
Female/male	784/920	154/232			
Hypertension			**1**	**0.010**	0.056
Absent/present	865/839	168/218			
Diabetes mellitus			**1**	NS	0.038
Absent/present	967/736	238/148			
Chronic kidney disease			**1**	**0.002**	0.069
Absent/present	1573/131	337/49			
Cardiovascular disease			**1**	**<0.001**	0.074
Absent/present	1573/129	336/50			
Severe chest CT findings			**1**	**<0.001**	0.233
Absent/present	1426/229	217/130			
Comorbidities			**3**	NS	0.054
0	497 (23.8%)	101 (28.6%)			
1	429 (49.1%)	97 (53.8%)			
2	443 (75.0%)	91 (79.3%)			
≥3	335 (95.4%)	97 (100.0%)			
Variants			**2**	**<0.001**	0.123[a]
Alpha	526	175			
Delta	583	116			
Omicron	595	95			
Duration of hospital stay (days)			**2074**	**<0.001**	0.384
Median	10.00	16.00			
IQR	8.00	11.00			
Range	0.00-104.00	1.00-128.00			
SII			**2088**	**<0.001**	0.199
Median	1014.00	1567.00			
IQR	1595.00	2597.00			
Range	0.00-720438.00	3.91-302.91			
SO_2 (%)			**2084**	**<0.001**	0.389
Median	94.00	91.00			
IQR	4.00	8.00			
Range	55.00-99.00	46.00-99.00			

Table 2. Continued					
Hemoglobin (g/dL)			**1881**	**<0.001**	0.177
Median	12.50	11.90			
IQR	2.73	2.85			
Range	5.00-135.00	5.80-17.00			
Hematocrit (%)			**2071**	**0.007**	0.089
Median	37.9	38.1			
IQR	7.70	300.00			
Range	11.50-509.00	18.00-506.00			
White blood cell count (x10^6 cells/L)			**2088**	**<0.001**	0.119
Median	7120.00	8030.00			
IQR	4930.00	6065.00			
Range	1.38-96000.00	2.35-151220.00			
Lymphocyte count (x10^9 cells/L)			**2088**	**<0.001**	0.278
Median	1060.00	770.00			
IQR	850.00	618.00			
Range	2.10-88270.00	100.00-144810.00			
Neutrophil count (x10^9 cells/L)			**2088**	**<0.001**	0.188
Median	5390.00	6985.00			
IQR	4480.00	5405.00			
Range	0.00-29180.00	550.00-30620.00			
Eozinophil count (x10^9 cells/L)			**2088**	**<0.001**	0.207
Median	0.20	0.00			
IQR	30.00	10.00			
Range	0.00-2420.00	0.00-610.00			
Platelet count (x10^3 cells/L)			**2088**	**<0.001**	0.163
Median	206.00	192.00			
IQR	111.00	91.00			
Range	11.00-1147.00	22.00-954.00			
Glucose (mg/dL)			**1989**	**<0.001**	0.165
Median	144.00	152.00			
IQR	99.58	109.00			
Range	48.00-3801.00	14.00-4123.00			
Creatinin (mg/dL)			**2000**	**<0.001**	0.432
Median	0.94	1.73			
IQR	0.53	2.25			
Range	0.10-231.00	0.32-96.00			
Lactate dehydrogenase (U/L)			**2073**	**<0.001**	0.453
Median	309.50	459.00			
IQR	168.25	328.00			

Table 2. Continued					
Range	44.00-5080.00	0.00-5200.00			
Procalcitonin (ng/mL)			**2042**	**<0.001**	0.651
Median	0.14	2.00			
IQR	0.30	10.72			
Range	0.01-33872.00	0.03-22682.00			
C-reactive protein (mg/L)			**2058**	**<0.001**	0.221
Median	88.00	178.00			
IQR	113.00	205.00			
Range	0.00-526.00	1.00-451.67			
D-dimer (µg/mL FEU)			**1989**	**<0.001**	0.487
Median	0.74	2.86			
IQR	1.19	4.83			
Range	0.00-99.00	0.01-89.00			
Fibrinogen (mg/dL)			**1902**	**<0.001**	0.172
Median	570.00	645.00			
IQR	198.00	242.00			
Range	152.00-1200.00	114.00-120.00			

df: Degree of freedom, SO_2: Early admission oxygen saturation, IQR: Interquartile range, CT: Computed tomography, SII: Systemic immune-inflammation index
[a]Chi-square test

Table 3. Regression analysis results of study parameters according to outcome

Independent variables	**B**	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% CI for EXP(B)**	
Variants			9,074	2	0.011			
Alpha variant	0.664	0.221	9,008	1	0.003	1,943	1,259	2,998
Delta variant	0.23	0.202	1,296	1	0.255	1,259	0.847	1.87
Presence of severe chest CT findings (+)	0.532	0.186	8,223	1	0.004	1,703	1,184	2.45
CKD (+)	0.996	0.232	18,451	1	p<0.001	2,708	1,719	4,266
Duration of hospital stay (days)	0.02	0.007	8.65	1	0.003	1.02	1,007	1,033
Age (years)	0.05	0.006	62,553	1	p<0.001	1,052	1,039	1,065
Admission SO_2 (%)	-0.079	0.015	25,739	1	p<0.001	0.924	0.897	0.953
LDH (U/L)	0.002	0	37,668	1	p<0.001	1,002	1,002	1,003
CRP (mg/L)	0.006	0.001	46,542	1	p<0.001	1,006	1,004	1,008
D-dimer (µg/mL FEU)	0.039	0.005	52,892	1	p<0.001	1.04	1,029	1,051
Constant	-0.759	1.57	0.234	1	0.629	0.468		

S.E.: Standard error, df: Degree of freedom, SO_2: Early admission oxygen saturation, CI: Confidence interval, CT: Computed tomography, CKD: Chronic kidney disease, LDH: Lactate dehydrogenase, CRP: C-reactive protein

group was significantly higher than that of the other two groups (p<0.05, both). Previous studies also showed a higher rate of alpha infections in males than in females (11), but the emergence of new mutant variants and/or vaccines somewhat affected these issues (12). We should mention that the rate of known comorbidities (HT, DM, CKD, and CVD) that could affect the course and outcome of this disease was also different between the study groups. This should also be considered [the presence of severe chest CT findings and mortality rate, and duration of hospital stay

were significantly higher in alpha variant group patients (in comparison to the other 2 groups) ($p<0.05$, all, and ES were 0.32, 0.12, and 0.08, respectively)] (12,13). Regarding the laboratory parameters, although most of them were significantly different between the groups, their ES was not significantly different (Table 1).

There was a significant difference in the study parameters of patients who survived or died from COVID-19 infection. Behind the statistical significance, most of these showed a somewhat high ES (Table 2). Regression analysis of all parameters that may affect the outcome of patients. As shown in Table 3, the presence of the Alpha variant infection was one of the important determinants of mortality. This variant increased the risk of mortality by 1.25 times. Previous studies also showed a high risk of hospitalization and death in patients with alpha variant COVID-19 infections. Significant differences were observed in the study parameters between COVID-19 patients who survived and those who succumbed to the infection. These differences were not only statistically significant but also demonstrated relatively high ES, as indicated in Table 2. To further explore the factors influencing patient outcomes, a regression analysis was conducted, considering all potential parameters. The results presented in Table 3 highlight the significance of alpha variant infection as a crucial determinant of mortality. Patients infected with the alpha variant faced a 1.25-fold higher risk of mortality. This finding aligns with previous studies that have also reported a heightened risk of hospitalization and death associated with the alpha variant of COVID-19. In a commentary by Cevik and Mishra (14). The severity of this variant-related COVID-19 infection is increased with ages more than 30 years. Additionally, this severity of infection is more pronounced in patients older than 65 years. In our patient data set, age was also a predictor of outcome. The median age of those patients who died was significantly higher than that of those who survived this infection in our study patients (70 versus 64 years old, $p<0.05$) (Table 2). This finding is also consistent with other published studies (14,15). Lung involvement is a predictor of the severity and outcome of this viral disease (16). Our study findings also showed increased mortality with increased severity of lung involvement as detected by chest CT (Table 2 and 3) (8). Previous studies from Türkiye and other countries have shown a poor outcome of COVID-19 in CKD patients (15,17,18). Our study results also support these findings. The presence of CKD in our study patients (regardless of the type of COVID-19 variant) increased the mortality risk by 1,719 times (Table 3). Although other predictors of mortality were determined in our study, the determination of the effect of CKD on the mortality of COVID-19 is of paramount importance that could help in planning the management and/or in planning similar studies in this field.

One of the important limitations of this study is that it was retrospective. Therefore, we could not assess the effect of the type of therapy on the outcome. The management of the disease was performed according to the Turkish Ministry of Health's guidelines applicable at the related periods and/or peaks of COVID-19 infection. The other limiting factor is not including intensive care unit (ICU) patients in this study. To decrease bias and incorrect data, we used data from our non-ICU pandemic services. This study has a notable limitation as it is retrospective in nature, which means that we were unable to evaluate the impact of different therapies on patient outcomes. The management of the disease followed the guidelines provided by the Turkish Ministry of Health during the relevant periods and peaks of COVID-19 infection. Another limitation is that the study did not include patients from the ICU. To mitigate potential biases and ensure accurate data, we relied on data obtained from non-ICU pandemic services.

CONCLUSION

Our study results determined unique useful early admission predictors of COVID-19 infection that could be used in different stages and variants of SARS-CoV-2 viral infection. These findings could be a pathfinder for clinicians and/or researchers dealing with this challenging contagious viral disease. The findings of our study have identified valuable predictors for early admission in COVID-19 infection, which can be applied across various stages and variants of SARS-CoV-2 viral infection. These results provide valuable guidance for clinicians and researchers involved in the management of this complex and highly contagious viral disease. They serve as a valuable resource for navigating the challenges posed by COVID-19.

ETHICS

Ethics Committee Approval: This retrospective study was approved by University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital's Clinical Research Ethics Committee (decision no: 2022-12-18, date: 20.06.2022).

Informed Consent: Informed consent was obtained from each subject before the study.

Authorship Contributions

Surgical and Medical Practices: D.Y., F.A., İ.Ö., M.H., Concept: D.Y., F.A., B.E., M.H., Design: D.Y., F.A., B.E., M.H., Data Collection or Processing: F.K., İ.Ö., Analysis or

Interpretation: F.A., B.E., F.K., M.H., Literature Search: F.A., E.Ş., F.K., İ.Ö., Y.E.Ö., H.G., M.H., Writing: F.A., E.Ş., Y.E.Ö., H.G., M.H.

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. Hursitoglu M, Isıksacan N, Erismis B, Karandere F, Kural A, Kumbasar AB, et al. In-vitro cytokine production and nasopharyngeal microbiota composition in the early stage of COVID-19 infection. Cytokine 2022;149:155757.
2. Papanikolaou V, Chrysovergis A, Ragos V, Tsiambas E, Katsinis S, Manoli A, et al. From delta to Omicron: S1-RBD/S2 mutation/deletion equilibrium in SARS-CoV-2 defined variants. Gene 2022;814:146134.
3. Tian D, Sun Y, Zhou J, Ye Q. The global epidemic of SARS-CoV-2 variants and their mutational immune escape. J Med Virol 2022;94:847-57.
4. Fan Y, Li X, Zhang L, Wan S, Zhang L, Zhou F. SARS-CoV-2 Omicron variant: recent progress and future perspectives. Signal Transduct Target Ther 2022;7:141.
5. Özüdoğru O, Bahçe YG, Acer Ö. SARS CoV-2 reinfection rate is higher in the Omicron variant than in the Alpha and Delta variants. Ir J Med Sci 2023;192:751-6.
6. Loucera C, Perez-Florido J, Casimiro-Soriguer CS, Ortuño FM, Carmona R, Bostelmann G, et al. Assessing the Impact of SARS-CoV-2 Lineages and Mutations on Patient Survival. Viruses 2022;14:1893.
7. The National Kidney Federation. CHRONIC KIDNEY DISEASE. 2022. Dr Oshini Shivakumar. https://www.kidney.org.uk/chronic-kidneydisease?gclid=Cj0KCQjw48OaBhDWARIsAMd966BxitxaUCdCjgeWjdhOAwPWStD41P9bPBZ74Ff6Nw-_vrGArG1LnjwaArUgEALw_wcB.
8. Yaltırık Bilgin E, Bilgin E, Fidan H, Çelenk Y, Tok T. Correlation of Clinical Course with Computed Tomography Findings and Biochemical Parameters at the Time of Admission in COVID-19 Patients. Turk J Anaesthesiol Reanim 2022;50:274-81.
9. Feng JF, Chen S, Yang X. Systemic immune-inflammation index (SII) is a useful prognostic indicator for patients with squamous cell carcinoma of the esophagus. Medicine (Baltimore) 2017;96:e5886
10. Erismis B, Karabela SN, Eksi F, Karandere F, Dogan B, Okay F, et al. Annual influenza vaccination effect on the susceptibility to COVID-19 infection. Cent Eur J Public Health 2021;29:14-7.
11. Agrawal H, Das N, Nathani S, Saha S, Saini S, Kakar SS, et al. An Assessment on Impact of COVID-19 Infection in a Gender Specific Manner. Stem Cell Rev Rep 2021;17:94-112.
12. Kahn F, Bonander C, Moghaddassi M, Rasmussen M, Malmqvist U, Inghammar M, et al. Risk of severe COVID-19 from the Delta and Omicron variants in relation to vaccination status, sex, age and comorbidities - surveillance results from southern Sweden, July 2021 to January 2022. Euro Surveill 2022;27:2200121.
13. Wilk-Sledziewska K, Sielatycki PJ, Uscinska N, Bujno E, Rosolowski M, Kakareko K, et al. The Impact of Cardiovascular Risk Factors on the Course of COVID-19. J Clin Med 2022;11:2250.
14. Cevik M, Mishra S. SARS-CoV-2 variants and considerations of inferring causality on disease severity. Lancet Infect Dis 2021;21:1472-4.
15. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med 2020;180:1345-55.
16. Kanne JP, Bai H, Bernheim A, Chung M, Haramati LB, Kallmes DF, et al. COVID-19 Imaging: What We Know Now and What Remains Unknown. Radiology 2021;299:E262-79.
17. Ozturk S, Turgutalp K, Arici M, Odabas AR, Altiparmak MR, Aydin Z, et al. Mortality analysis of COVID-19 infection in chronic kidney disease, haemodialysis and renal transplant patients compared with patients without kidney disease: a nationwide analysis from Turkey. Nephrol Dial Transplant 2020;35:2083-95.
18. Pecly IMD, Azevedo RB, Muxfeldt ES, Botelho BG, Albuquerque GG, Diniz PHP, et al. COVID-19 and chronic kidney disease: a comprehensive review. J Bras Nefrol 2021;43:383-99.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:382-388
DOI: 10.4274/BMJ.galenos.2023.2023.4-3

Research

Non-infectious Causes of Blood Transfusion Reactions: A Tertiary Hospital Review

Kan Transfüzyon Reaksiyonlarının Bulaşıcı Olmayan Nedenleri: Bir Üçüncü Basamak Hastane İncelemesi

Şemsi Nur Karabela[1], Esra Canbolat Ünlü[1], Serap Pamak Bulut[2], Deniz Yılmaz[3], Serap Altungayular[4], Kürşad Nuri Baydili[5], Rüveyda Alacahan[6], İbrahim Taşpolat[4], Habip Gedik[1], Kadriye Kart Yaşar[1]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Surgery, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
[4]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Blood Center, İstanbul, Türkiye
[5]University of Health Sciences Türkiye, Vocational School of Health Services, Department of Management and Organization, İstanbul, Türkiye
[6]University of Health Sciences Türkiye, Vocational School of Health Services, İstanbul, Türkiye

ABSTRACT

Objective: Blood transfusion is a life-saving medical intervention. Transfusion reactions are undesirable consequences of this intervention and may present with various findings. Using data from our hospital and hemovigilance procedures that included electronic recording, our aim was to evaluate non-infectious transfusion reactions.

Methods: We present reaction data from electronic recordings of blood products transfused between January 2017 and December 2021. Gender, age, symptoms and findings, blood pressure, fever, respiratory and heart rates before and after transfusion were analyzed according to reaction types. Reactions were classified according to clinicians definition. Analysis of the data was carried out using the SPSS 25 package program.

Results: While allergic transfusion reactions and febril nonhemolitic transfusion reactions were common transfusion reactions, the most common reaction products were fresh frozen plasma, erythrocyte suspension and platelet suspension respectively. Chills, restlessness, fever, were common signs and symptoms. While allergic transfusion reactions were higher in pediatric patients, there was no difference between genders. The high number of patients who had a previous transfusion among the patients who developed a reaction suggested that exposure did not reduce the risk. More notifications were made after the use of electronic records than in previous years.

Conclusion: Electronically recorded hemovigilance data can contribute to an increase in accurate classification and reporting of transfusion reactions and monitoring of blood processes.

Keywords: Transfusion reactions, allergic reactions, febrile reactions, electronic hemovigilance, transfusion related adverse events

ÖZ

Amaç: Kan transfüzyonu hayat kurtarıcı bir tıbbi müdahaledir. Transfüzyon reaksiyonları bu girişimin istenmeyen sonuçlarıdır ve çeşitli bulgularla karşımıza çıkabilir. Amacımız; hastanemizden elde edilen verileri ve elektronik kaydı içeren hemovijilans prosedürlerini kullanarak enfeksiyöz olmayan transfüzyon reaksiyonlarını değerlendirmekti.

Gereç ve Yöntem: Ocak 2017 ile Aralık 2021 tarihleri arasında transfüze edilen kan ürünlerinin elektronik kayıtlarından elde edilen reaksiyon verileri incelendi. Transfüzyon öncesi ve sonrası cinsiyet, yaş, semptom ve bulgular, kan basıncı, ateş, solunum ve kalp hızları reaksiyon tiplerine göre analiz edildi. Reaksiyonlar klinisyen tanımına göre sınıflandırıldı. Verilerin analizi SPSS 25 paket programı kullanılarak yapılmıştır.

Bulgular: Alerjik transfüzyon reaksiyonları ve hemolitik olmayan febril transfüzyon reaksiyonları sık görülen transfüzyon reaksiyonları iken, en sık reaksiyon görülen ürünler sırasıyla taze donmuş plazma, eritrosit süspansiyonu ve trombosit süspansiyonuydu. Titreme, huzursuzluk, ateş yaygın

Address for Correspondence: Şemsi Nur Karabela, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Türkiye
Phone: +90 505 562 84 95 E-mail: semsinurk@hotmail.com ORCID ID: orcid.org/0000-0003-2562-3004

Cite as: Karabela ŞN, Canbolat Ünlü E, Pamak Bulut S, Yılmaz D, Altungayular S, Baydili KN, Alacahan R, Taşpolat İ, Gedik H, Kart Yaşar K. Non-infectious Causes of Blood Transfusion Reactions: A Tertiary Hospital Review. Med J Bakirkoy 2023;19:382-388

Received: 22.04.2023
Accepted: 17.10.2023

belirti ve semptomlardı. Alerjik transfüzyon reaksiyonları pediatrik hastalarda daha fazla görülürken, cinsiyetler arasında fark yoktu. Reaksiyon gelişen hastalar arasında daha önce transfüzyon geçirmiş hasta sayısının fazla olması maruziyetin riski azaltmadığını düşündürdü. Elektronik kayıtların kullanılmasından sonra geçmiş yıllara göre daha fazla bildirim yapılmıştır.

Sonuç: Elektronik olarak kaydedilen hemovijilans verileri, transfüzyon reaksiyonlarının doğru sınıflandırılmasında ve raporlanmasında ve kan süreçlerinin izlenmesinde artışa katkıda bulunabilir.

Anahtar Kelimeler: Transfüzyon reaksiyonları, alerjik reaksiyonlar, ateşli reaksiyonlar, elektronik hemovijilans, transfüzyonla ilişkili istenmeyen olaylar

INTRODUCTION

Transfusion reactions (TRs) are adverse events associated with the transfusion of blood products and findings such as fever, chills, pruritus, and urticaria are common (1). Reactions after blood transfusion can be listed as acute hemolytic transfusion reactions (AHTR), febrile non-hemolytic transfusion reactions (FNHTR), allergic transfusion reaction (ATR), transfusion related acute lung injury (TRALI) and transfusion associated circulatory overload (TACO) (2-4).

AHTRs are rare life-threatening reactions including fever, chills, flank pain and leakage from intravenous sites caused by ABO incompatibility due to labeling errors or reactions against the alleles of other red blood cell antigen systems (2).

FNHTRs including chills, flushing, headache, tachycardia, mild dyspnea, and nausea/vomiting defined as the body temperature is ≥38 °C during or within 4 hours or a rising more than 1 °C from the onset of transfusion without symptoms of hemolysis and no evidence of infectious/ environmental reason (3).

ATR is a common form of acute TR and present with by urticaria, pruritus, erythematous rash, angioedema, bronchospasm, and/or hypotension (4). The best known and relatively rare pulmonary complications of transfusion are TRALI (<0.01%) and TACO (<1%). TACO is a type of pulmonary edema due to volume excess or circulatory overload. TRALI is a life-threatening form of acute lung injury that includes fever, chills, and respiratory distress (5).

Electronic records are effectively used for routine health data such as demographic information, diagnosis, imaging and laboratory findings in healthcare services (6). Hemovigilance systems also take advantage of this opportunity through intrahospital and national networks. The use of electronic technologies can speed up data collection and feedback thus enabling hemovigilance centers to access transfusion-related information early. It has been reported that, electronic records powered by clinical decision support systems increase the verified reaction reporting (7,8). It has been reported that repeated exposure, rather than the total volume of transfused blood product, may influence the incidence of ATRs (9).

In addition the incidence of reactions, when evaluated per patient transfused, may differ from that calculated based on the number of blood products (10).

The aim of this retrospective study is to evaluate blood transfusion reactions in a tertiary care hospital based either on product or patient via the data of hemovigilance center. The data obtained after the electronic hemovigilance records were started to use were compared with the previous period. In addition, the changes in the clinical findings of the patients before and after the transfusion and the relationship between the reactions and repeated exposure are presented.

METHODS

A total of 200,256 transfusion forms reported to the hemovigilance center in 2017-2021 were evaluated retrospecvtively. Reactions were classified as "Anaphylactic, AHR, ATR, FNHTR, TACO, TRALI and Unidentified" according to clinicians' definition. The data of the patients such as gender, age, symptoms and findings, blood pressure, fever, respiratory and heart rates before and after transfusion were analyzed according to reaction types.

Figure 1 depicts the flow of requests and notifications for blood products at our institution. The feedback rate in our hospital is over 98% (11). Reaction definitions have been categorized by clinicians according to Turkish National Hemovigilance guidelines (12). The data of our study was obtained from these digital forms by two different researchers.

Transfused blood products were classified as erythrocyte suspension (ES), fresh frozen plasma (FFP), whole blood, platelet suspensions (PSs) (random, pooled, apheresis), cryoprecipitate and others. TRs incidence according to blood product types was defined as the number of reactions divided by the total number of products transfused and the number of patients. For each TR, the average of the clinical findings (blood pressure, body temperature, respiration

and heart rate) was taken into account whether there was a difference between before and after transfusion. Types of reactions and causative blood products were listed according to previous transfusion status. Hamidiye Clinical Research Ethics Committee of Health Sciences University approval was obtained for the research and ethical rules were followed (decision no: 35/20, date: 19.11.2021).

Statistical Analysis

Analysis of the data was carried out using the SPSS 25 package program. Frequency and percentage values for qualitative variables, median, minimum and maximum values for quantitative variables are presented. Chi-square test was used for comparisons between two qualitative variables. In order to compare the difference before and after transfusion, the difference score was calculated for the discrete variables and the percentage change for the continuous variables. The Kruskal-Wallis H test was used for comparisons between qualitative and quantative variables containing more than two categories. If there was a significant difference in the Kruskal-Wallis H test, the categories were compared in pairs with the Mann-Whitney U test. In the study, the type error rate was taken as 0.05.

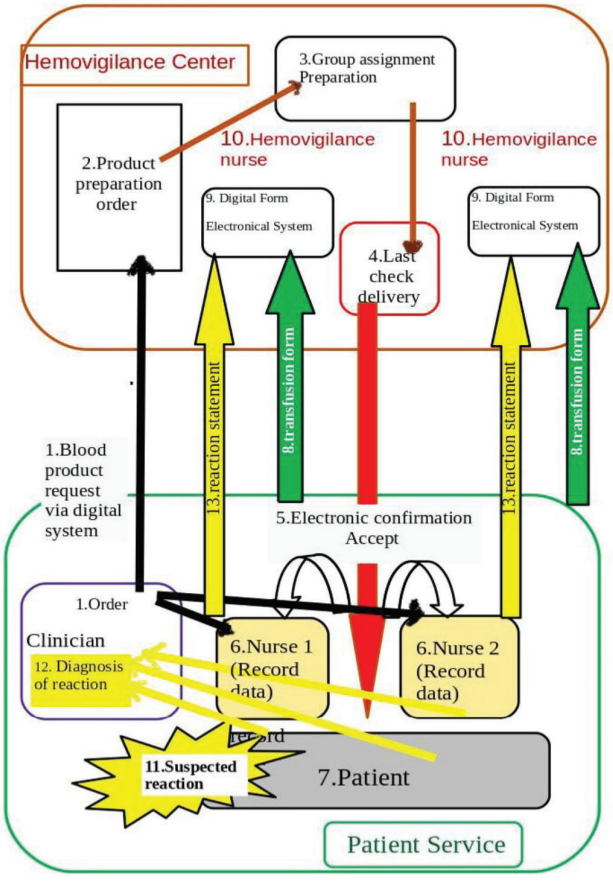

Figure 1. Demand and feedback flow for blood products. 1. The blood product is digitally ordered from the Hemovigilance Center for the patient. 2-4. When the group of the blood product is verified by the system, it is approved and delivered to the service nurse. 5. The blood product is received by scanning the barcode. 6. Transfusion is started under the control of two nurses. 7. The vital signs of the patient are recorded electronically every 15 minutes. 8. When the transfusion is finished, the form is transmitted electronically to the hemovigilance center. 9-10. The hemovigilance nurse evaluates electronic forms. 11,12. If a transfusion reaction is suspected, the clinician is informed. The reaction is diagnosed. 13. The characteristics of the reaction, the type of blood product, the patient's symptoms and signs are recorded. It is delivered to the transfusion center through the system. Steps 9 and 10 are repeated

RESULTS

Between January 2017 and December 2021, 43,516 patients received 200,256 blood product transfusions in our hospital. The frequency of transfused blood products is 46.2% with ES, 37.2% with FFP and 15% with PS, respectively. A total of 261 TRs were reported in 234 patients. Table 1 displays the distribution by product.

TRs were most frequently seen with FFP (48.3%), followed by ES (41.7%) and PSs (9.6%). When evaluated according to product, the incidence of TR was found to be the highest (0.17%) with FFP and whole blood. When evaluated according to the number of transfused patients, the incidences of reactions were 0.72% in FFP, 0.66% in random PSs and 0.44% in ES.

The mean age of the patients who developed a TR was 46.56 (±24.15) years. The most common TR was ATR (63.9%) and FHTR (13%). Types of reactions are shown in Figure 2. There were no AHTR and fatal reaction. In 44 patients (16.85%) TRs could not be classified. Mild allergic reactions appeared to be the most common TR for each blood product.

Between 2017 and 2021, the annual TR numbers that were recorded by years were 42, 76, 66, 41, and 36. Notifications grew from 22 to 52 on average per year. In patients who experience a TR, chills (17.9%), restlessness (6%), fever (16.2%), skin rash (15.7%), and itching (7.2%) were the most prevalent symptoms and findings (Figure 3).

Table 2 compares vital indicators before and after transfusion in accordance with the different forms of reaction. Patients who were classified as having a febrile reaction had higher post-transfusion fever levels than other patients ($p<0.001$).

In patients with mild allergic reaction, pre-transfusion systolic arterial blood pressure was lower than the others ($p=0.018$). Generally, the type of reaction could not be defined in patients with a significant increase in pulse values after transfusion ($p=0.002$). There was no difference between reaction types in terms of other variables examined. There was no difference in reaction types according to gender ($p=0.34$). However, mild allergic reactions were more common in pediatric patients (n=29, 87.9%) compared to adults (n=129, 66.5%) ($p=0.044$). One hundred and fifty-nine

Table 1. Numbers of reactions and ıncidence according to blood products

Blood component	N. of transfused products	N. of reactions	Incidence of product (%)	N. of transfused patients	N. of patients who had a reaction	Incidence of patient-reaction (%)
Erythrocyte suspension	92,609	109	0.12	23,580	105	0.44
Fresh frozen plasma	74,502	126	0.17	14,674	107	0.72
Platelet suspension (random)	22,304	19	0.08	2,400	16	0.66
Platelet suspension (pooled)	5,748	4	0.07	1,411	4	0.28
Cryoprecipitate	2,176	0	0	247	0	0
Platelet suspension (apheresis)	2,130	2	0.09	647	2	0.3
Whole blood	574	1	0.17	415	1	0.24
Other*	213	0	0	142	0	0
Total	**200,256**	**261**	**0.13**	**43,516**	**234****	**0.53**

N.: Number, *Apheresis granulocyte, apheresis immune fresh frozen plasma, **One patient had a reaction with both erythrocyte suspension and fresh frozen plasma

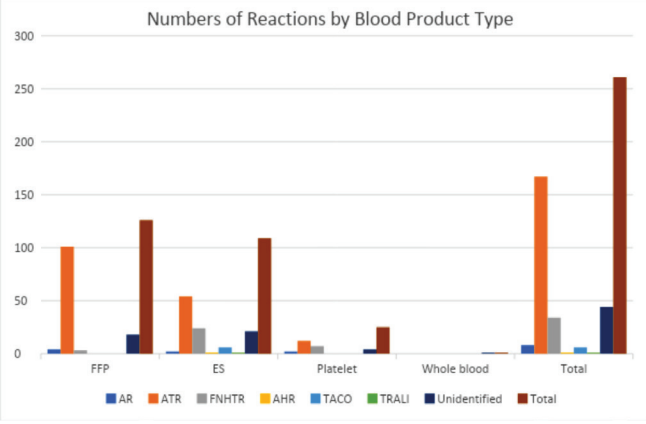

Figure 2. Numbers of reactions by blood product type
AR: Anaphylactic reaction, ATR: Allergic transfusion reaction, FNHTR: Febrile non-hemolytic transfusion reaction, AHR: Acute hemolytic reaction, TACO: Transfusion-associated circulatory overload, TRALI: Transfusion-related acute lung injury, FFP: Fresh frozen plasma, ES: Erythrocyte suspension

(67.9%) of the 234 individuals who experienced a response had previously received a blood product transfusion. Table 3 contains distributions by products and reaction.

DISCUSSION

While the risk of infection in transfusions is reduced thanks to the good examination of donors, non-infectious complications continue to be a clinical problem. These complications are usually TRs (13). The information gathered by reporting the reactions to the hospital's hemovigilance unit may be useful in the future.

Hemovigilance is dependent on the nurse and clinician notifying the transfusion center of information pertaining to transfusions. The typical transfusion process or the diagnostic results of an emerging response may be included in this information. The formats in which the information is delivered, however, take time to get to the center. Data collection and feedback can be accelerated by the deployment of electronic technologies that allow hemovigilance centers to quickly access transfusion-related information (7).

The hemovigilance system's inclusion of a decision support system and the development of electronic algorithms in response to the findings boost the reporting of TR (6). There is no such warning system in our study. However, the requirement to complete the form on the computer screen and the standardization of reporting, including clinical findings, provided for more frequent and extensive reporting of reactions.

While the rates were between 0.05% and 0.18% in previous studies of the incidence of reactions, this rate was found to be 0.13% in our study (14,15). We think that the reason why no hemolytic reaction was observed in our follow-ups is our strict control strategies. Our findings support studies showing that the ratio of reactions by product or patient changes the incidence results (10).

Our research revealed that non-serious transfusion responses shared similar symptoms. Clinicians may have difficulty correctly identifying the reaction as a result.

According to the literature, febrile nonhemolytic and allergic reactions are reported more frequently than other (15-20).

In line with the literature, we discovered that allergic reactions to transfusions occurred more frequently (0.4%)

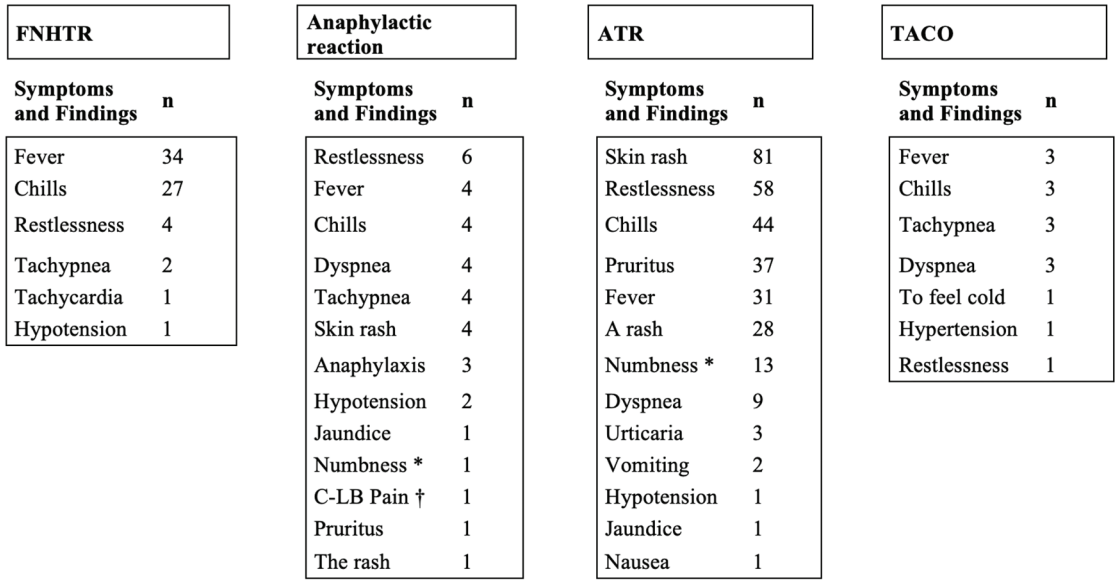

Figure 3. Symptoms and findings

FNHTR: Febrile non-hemolytic transfusion reaction, ATR: Allergic transfusion reaction, TACO: Transfusion-associated circulatory overload, TRALI: Transfusion-related acute lung injury, *Numbness (in the finger and around the mouth), †Chest and lower back pain

Table 2. Clinical findings by reactions

	FNHTR	ATR	Unidentified reaction	Kruskal-Wallis H	p-value
Temperature before transfusion/°C	36.7 (36-38,8)	36.5 (35.4-38)	36.6 (36-37.2)	3.267	0.195
Temperature after transfusion/°C	37.8 (36.2-39.1)	36.6 (35.5-39.4)	36.7 (35.6-39)	35.283	<0.001*
Pre-transfusion systolic blood pressure/ mmHg	117 (66-154)	112.5 (65-189)	120 (65-180)	8.001	0.018*
Pre-transfusion diastolic blood pressure/ mmHg	70 (39-92)	70 (10-94)	70 (22-85)	1.591	0.451
Post-transfusion systolic blood pressure/ mmHg	117 (66-177)	118 (65-186)	118.5 (60-175)	0.305	0.858
Post-transfusion diastolic blood pressure/ mmHg	70 (28-93)	71 (24-100)	70 (20-90)	4.144	0.126
Pre-transfusion peripheral pulse beats/ minute	88 (73-150)	87 (21-179)	91.5 (62-172)	5.062	0.080
Post-transfusion peripheral pulse beats/ minute	92 (75-172)	88 (18-193)	100.5 (60-196)	12.554	0.002*
Pre-transfusion respiratory rate/minute	20 (15-58)	20 (12-52)	20 (14-98)	0.882	0.643
Post-transfusion respiratory rate/minute	20 (16-60)	20 (12-61)	20 (14-98)	2.473	0.290
Difference temperature/°C	2,459 (-0.79-7.44)	0 (-100-6.94)	0.2743 (-2.2-5.98)	29.332	<0.001*
Difference systolic/mmHg	3.7736 (-45.9-55)	4.6537 (-100-96.63)	-7.5599 (-50-84.62)	5.665	0.059
Difference diastolic/mmHg	6.9444 (-53.33-1.54)	0 (-100-600)	-6.4583 (-71.43-263.64)	5.090	0.078
Difference peripheral pulse beats/minute	2 (-8-24)	0 (-83-47)	4 (-35-76)	6.865	0.032*
Difference respiratory rate/minute	0 (-2-5)	0 (-16-13)	0 (-5-33)	1.240	0.538

*p<0.05 Kruskal-Wallis H: Kruskal-Wallis H test calculation value. ATR: Allergic transfusion reaction, FNHTR: Febrile non-hemolytic transfusion reaction

Table 3. Previous exposure to blood products and reaction type

		Previously transfused patient (n)	Patient not transfused before (n)
Blood product	ES	77	28
	FFP	65	41
	PS	17	5
	Whole blood	0	1
Total		**159**	**75**
Reaction type	ATR	99	46
	FNHTR	22	8
	Anaphylactic	8	0
	TACO	4	1
	TRALI	1	0
	AHR	1	0
	Unidentified	24	20
Total		**159**	**75**

AR: Anaphylactic reaction, ATR: Allergic transfusion reaction, FNHTR: Febrile non-hemolytic transfusion reaction, AHR: Acute hemolytic reaction, TACO: Transfusion-associated circulatory overload, TRALI: Transfusion-related acute lung injury, FFP: Fresh frozen plasma, ES: Erythrocyte suspension, PS: Platelet suspensions

than other reactions. According to several research, the incidence of allergic responses may exceed 3% (20-22). The frequency of ATR development linked with the use of these products is related to the highest incidence of responses following transfusions of whole blood and FFP. It is known that plasma proteins play a role in the reactions. TR risk is increased by recipient features, such as atopic susceptibility and high immunoglobulin E levels (21).

To minimize whole blood responses, it has been deemed crucial to carry out the proper predonation screening, particularly by assessing mean blood pressure (23). One patient experienced a reaction following a transfusion of whole blood, however the type of reaction could not be defined. We suspected that low systolic blood pressure before to donation would be a risk factor for allergic reactions when we assessed the systolic and diastolic blood pressures of our patients with other reactions.

Febrile nonhemolytic reactions were found to be lower than the literature (28-61%) (22,24). In the presence of symptoms such as rash and redness, it is possible to define an allergic reaction and also fever can be seen in other reactions. In the presence of additional findings, it was thought that clinicians were undecided about the type of reaction. Unfortunately; the similarity of signs and symptoms in conditions such as tremor, restlessness, itching resulted in the unclassification of the reaction in some patients. Anaphylactic reactions which is a severe state of allergic reactions, and serious reactions such as TACO, TRALI and hemolytic reactions were also rare in our hospital comparing with the others (5,25).

In 44 patients (16.85%) TRs could not be classified. It is a high number that the reaction could not be classified in 44 patients. Despite the standards for classification, this high rate may be due to the confusion in the findings and the clinician's lack of knowledge in the definition of TR.

Our results were consistent with earlier research that did not discover a relationship between gender and reaction development (22,24,26). Having a previous transfusion history does not eliminate the risk of ATRs (27). Patients who had previously received transfusions accounted for 67.9% of our reported responses. This bolsters the idea that individuals who have previously received blood products may experience transfusion responses.

The use of retrospective hemovigilance data, diagnosis by various doctors, and single-center design are the study's weaknesses. A comparison with those who did not develop a reaction was also impossible because only the transfusion exposure of those who experienced a reaction was known.

CONCLUSION

In our investigation, we demonstrated that despite good classification, doctors may struggle to differentiate between reactions because of overlapping clinical symptoms. Allergic TRs were thought to be common in patients with low blood pressure. Our results confirm that the use of electronic technology and the implementation of a rigorous hemovigilance system can facilitate TR follow-up by expediting reporting. The monitoring of TRs is crucial despite the serious reactions declining with excellent medical procedures.

ETHICS

Ethics Committee Approval: Study was approved by the Hamidiye Clinical Research Ethics Committee of Health Sciences University (decision no: 35/20, date: 19.11.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: Ş.N.K., E.C.Ü., S.P.B., H.G., K.K.Y., Design: Ş.N.K., E.C.Ü., S.P.B., H.G., Data Collection or Processing: E.C.Ü., D.Y., S.A., K.N.B., R.A., İ.T., Analysis or Interpretation: D.Y., S.A., K.N.B., R.A., İ.T., Literature Search: Ş.N.K., E.C.Ü., S.P.B., D.Y., S.A., K.N.B., R.A., İ.T., H.G., K.K.Y., Writing: Ş.N.K., E.C.Ü., K.K.Y.

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. Panch SR, Montemayor-Garcia C, Klein HG. Hemolytic Transfusion Reactions. N Engl J Med 2019;381:150-62.
2. Tobian AA, Savage WJ, Tisch DJ, Thoman S, King KE, Ness PM. Prevention of allergic transfusion reactions to platelets and red blood cells through plasma reduction. Transfusion 2011;51:1676-83.
3. Pritam Singh A. Immune-Mediated Chronic Transfusion Reactions. Immunohematology and Blood Banking : Principles and Practice. Singapore: Springer; 2020;20-208.
4. Özçelik F, Işıtmangil G. The Importance of Human Leukocyte Antigens, Complements and Immune System in Transfusion Medicine. Kan Bankacılığı ve Transfüzyon 2021;4:66-73.
5. Pelit NB. Non-Immune Reactions and Complications of Transfusion. Kan Bankacılığı ve Transfüzyon 2021;4:98-101.
6. Villamin C, Bates T, Mescher B, Benitez S, Martinez F, Knopfelmacher A, et al. Digitally enabled hemovigilance allows real time response to transfusion reactions. Transfusion 2022;62:1010-8.
7. Poisson LJ, O'Leary MF. Improving our reaction time - Using technology to identify transfusion reactions sooner. Transfusion 2022;62:923-7.
8. Lim YA, Kim J, Park C. Early recognition of possible transfusion reactions using an electronic automatic notification system for changes in vital signs in patients undergoing blood transfusions. Transfusion 2020;60:1950-9.
9. Kato H, Nakayama T, Uruma M, Okuyama Y, Handa M, Tomiyama Y, et al. Repeated exposure rather than the total volume of transfused components may influence the incidence of allergic transfusion reactions. Transfusion 2015;55:2576-81.
10. Kato H, Uruma M, Okuyama Y, Fujita H, Handa M, Tomiyama Y, et al. Incidence of transfusion-related adverse reactions per patient reflects the potential risk of transfusion therapy in Japan. Am J Clin Pathol 2013;140:219-24.
11. Karabela ŞN, Altungayular S, Taşpolat İ, Baydili KN, Kart Yaşar K. Monitoring and Transfusion Nursing Practices with Electronic Record in Blood Transfusion Process Management. Med Bull Haseki 2019;57:310-8.
12. Ertuğrul Örüç N, Yenicesu İ, Öztürk A, Kodaloğlu Temur Ü. Ulusal Hemovijilans Rehberi. 2020;47-56. https://shgmkanhizmetleridb.saglik.gov.tr/Eklenti/37016/0/ulusal-hemovijilans-rehberi-versiyon-2pdf.pdf.
13. Goel R, Tobian AAR, Shaz BH. Noninfectious transfusion-associated adverse events and their mitigation strategies. Blood 2019;133:1831-9.
14. Kumar P, Thapliyal R, Coshic P, Chatterjee K. Retrospective evaluation of adverse transfusion reactions following blood product transfusion from a tertiary care hospital: A preliminary step towards hemovigilance. Asian J Transfus Sci 2013;7:109-15.
15. Vasudev R, Sawhney V, Dogra M, Raina TR. Transfusion-related adverse reactions: From institutional hemovigilance effort to National Hemovigilance program. Asian J Transfus Sci 2016;10:31-6.
16. Delaney M, Wendel S, Bercovitz RS, Cid J, Cohn C, Dunbar NM, et al. Transfusion reactions: prevention, diagnosis, and treatment. Lancet 2016;388:2825-36.
17. Ikebe E, Matsuoka S, Tanaka A, Yonemura Y, Fujii Y, Ohsaka A, et al. Reduction in adverse transfusion reactions with increased use of washed platelet concentrates in Japan-A retrospective multicenter study. Transfus Apher Sci 2019;58:162-8.
18. Liker M, Bojanić I, Plenković F, Lukić M, Tomac G, Raos M, et al. Platelet transfusion practice and related transfusion reactions in a large teaching hospital. Transfus Clin Biol 2022;29:37-43.
19. Sönmezoğlu M. Hemovijilans. Ceran N, editör. Kan Bankacılığı ve Transfüzyon. 1. Baskı. Ankara: Türkiye Klinikleri; 2021. p. 108-12.
20. Pektas G, Çetin D. Transfüzyon İlişkili İstenmeyen Reaksiyonların 7 Yıllık Retrospektif Analizi: Tek Merkez Deneyimi. Abant Tip Dergisi 2021;10:47-53.
21. Savage WJ. Transfusion Reactions. Hematol Oncol Clin North Am 2016;30:619-34.
22. Sharma DK, Datta S, Gupta A. Study of acute transfusion reactions in a teaching hospital of Sikkim: A hemovigilance initiative. Indian J Pharmacol 2015;47:370-4.
23. Prakash S, Das PK, Mishra D, Ray GK, Routray S, Naik A, et al. Incidence and risk predictors analysis of adverse donor reactions in whole blood donation. Transfus Clin Biol 2020;27:207-12.
24. Grandi JL, Grell MC, Areco KCN, Barbosa DA. Hemovigilance: the experience of transfusion reaction reporting in a Teaching Hospital. Rev Esc Enferm USP 2018;52:e03331.
25. Hirayama F. Current understanding of allergic transfusion reactions: incidence, pathogenesis, laboratory tests, prevention and treatment. Br J Haematol 2013;160:434-44.
26. Azizi S, Tabary SZ, Soleimani A. Prevalence of acute blood transfusion reactions in Mazandaran Heart Center, Sari, Iran, 2010-2012. Med Arch 2014;68:137-9.
27. Kato H, Nakayama T, Uruma M, Okuyama Y, Handa M, Tomiyama Y, et al. A retrospective observational study to assess adverse transfusion reactions of patients with and without prior transfusion history. Vox Sang 2015;108:243-50.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:389-396
DOI: 10.4274/BMJ.galenos.2023.2023.3-21

Research

Can Native Thiol Levels be an Indicator to Determine the Severity of COVID-19 Cases?

Nativ Tiyol COVİD-19 Olgularının Şiddetini Tespit Etmede Belirteç Olarak Kullanılabilir mi?

Alev Kural[1], Murat Doğan[2], Şebnem Tekin[1], Aysun Toker[3], Keziban Doğan[4]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Biochemistry, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Türkiye
[3]Acıbadem Labmed Laboratory, İstanbul, Türkiye
[4]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Türkiye

ABSTRACT

Objective: To investigate the possible relationship between the severity of the disease and some oxidant-antioxidant markers in patients diagnosed with coronavirus disease-2019 (COVID-19).

Methods: A total of 130 cases with a diagnosis of COVID-19 were included in the study, classified as severe (group 1, n=65) and mild/moderate (group 2, n=65) and control group (group 3, n=54). Routine laboratory methods were used to analyze serum C-reactive protein, D-dimer, procalcitonin, and ferritin levels. In addition, the levels of oxidants, including malondialdehyde (MDA) and myeloperoxidase (MPO), as well as antioxidants, such as glutathione peroxidase (Gpx), superoxide dismutase (SOD), uric acid, and native thiol, were analyzed. The descriptive statistics of continuous variables were reported as the median with a range of minimum to maximum values. Furthermore, statistical tests such as the Kolmogorov-Smirnov and Mann-Whitney U tests were used. The chi-square test was used to investigate any statistical associations between groups and other categorical independent variables. To determine the significance, analysis of covariance (ANCOVA) was performed.

Results: The results showed that both group 1 and group 2 COVID-19 patients had considerably higher levels of routine laboratory tests than the control group ($p<0.001$). Furthermore, significantly lower levels of native thiol were found in both groups 1 and 2 compared with the control group ($p<0.001$ for both). In addition, a significant difference was observed between group 1 and group 2, with group 1 showing markedly lower levels of native thiol ($p<0.001$).

Conclusion: We concluded that the oxidative stress indicators MDA and MPO and the antioxidant indicators Gpx and SOD cannot be used to determine the severity of COVID-19, but decreasing natural thiol levels can be an indicator of disease severity in this population. In addition, these data may be important in explaining the mechanism of N-acetylcysteine therapy in COVID-19 cases.

Keywords: Native thiols, COVID-19, malondialdehyde, myeloperoxidase, superoxide dismutase, glutathione peroxidase

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVİD-19) tanısı alan olgularda hastalığın şiddeti ile bazı oksidan-antioksidan belirteçler arasındaki olası ilişkinin araştırılmasıdır.

Gereç ve Yöntem: Toplam 130 COVİD-19 tanılı olgu çalışmaya dahil edildi, semptomlarına göre şiddetli (grup 1, n=65) ve hafif/orta (grup 2, n=65) ve kontrol grubu (grup 3, n=54) olarak sınıflandırıldı. Serum C-Reaktif protein, D-dimer, prokalsitonin ve ferritin düzeyleri rutin laboratuvar yöntemleri ile analiz edildi. Oksidan malondialdehit (MDA), miyeloperoksidaz (MPO) ve antioksidanlar glutatyon peroksidaz (Gpx), süperoksit dismutaz (SOD), ürik asit ve doğal tiyol seviyeleri de analiz edildi. Sürekli değişkenler için tanımlayıcı istatistikler medyan (minimum-maksimum) olarak sunuldu ve ayrıca Kolmogorov-Smirnov, Mann-Whitney U testleri de kullanıldı. Gruplar ve diğer kategorik bağımsız değişkenler arasındaki istatistiksel ilişkiler ki-kare testi kullanılarak test edildi. Anlamlılığın değerlendirilmesi için kovaryans analizi (ANCOVA) kullanıldı.

Address for Correspondence: Alev Kural, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Biochemistry, İstanbul, Türkiye
Phone: +90 532 495 27 82 E-mail: alevkural@hotmail.com ORCID ID: orcid.org/0000-0003-1459-4316

Cite as: Kural A, Doğan M, Tekin Ş, Toker A, Doğan K. Can Native Thiol Levels be an Indicator to Determine the Severity of COVID-19 Cases?. Med J Bakirkoy 2023;19:389-396

Received: 18.04.2023
Accepted: 18.12.2023

Bulgular: COVİD-19 tanılı grup 1 ve grup 2 olgularda rutin laboratuvar testleri kontrol grubuna göre yüksek bulundu (p<0,001). Ayrıca hem grup 1 hem grup 2'de kontrol grubuna kıyasla daha düşük nativ tiyol düzeyleri saptanmıştır (her ikisi için de p<0,001). Buna ek olarak grup 1 ve grup 2 arasında anlamlı bir fark gözlendi. Grup 1 nativ tiyol değerleri belirgin olarak düşüktü (p<0,001).

Sonuç: Oksidatif stres göstergelerden MDA ve MPO'yu ve antioksidan göstergeleriden SOD ve Gpx'in COVİD-19'un şiddetini belirlemede kullanılamayacağı ancak azalan doğal tiyol seviyelerinin bu popülasyonda hastalık şiddetinin bir göstergesi olabileceği kanısına ulaştık. Ayrıca bu veri COVİD-19 olgularında N-asetilsistein tedavisinin mekanizmasını açıklamada da önemli olabilir.

Anahtar Kelimeler: Nativ tiyol, COVİD-19, malondialdehit, miyeloperoksidaz, süperoksit dismutaz, glutatyon peroksidaz

INTRODUCTION

Coronavirus disease-2019 (COVID-19) was initially identified in Wuhan, China, and quickly became a global pandemic, spreading to various parts of the world. Although most COVID-19 patients do not require hospitalization, moderate or severe conditions can be detected in a minority of cases (1). In COVID-19 pathophysiology, the host's response to the infection leads to respiratory dysfunction and the activation of multisystemic inflammatory responses (2,3). The progression of COVID-19 can lead to a wide variety of clinical symptoms, ranging from no obvious symptoms to respiratory failure and dysfunction of multiple organs. It is known that some laboratory markers, such as hematological parameters (especially lymphopenia), cytokines, and liver enzymes that might be useful in indicating a progression from mild to severe disease, are used in daily practice, and some inflammatory markers have diagnostic value for disease severity and fatality (4-10). Despite extensive research, there is still debate surrounding the impact of inflammatory markers on the pathogenesis of COVID-19. The clinical course of COVID-19 depends on several factors such as cytokine storm, excessive inflammation, and low blood oxygen levels (11,12).

C-reactive protein (CRP) is an important acute phase reactant induced by IL-6. Inflammation, infection, and cellular injury cause a rapid increase in the serum levels of CRP. CRP levels are increased in COVID-19 patients and indicate a strong correlation with prognosis and disease severity (13-15).

Micronutrient iron is vital for the survival of pathogens; hence, the immune system of the host may limit the accessibility of iron during infections as a protective measure. This, in turn, leads to elevated levels of ferritin. Under inflammatory conditions caused by superoxide radicals, iron is released from ferritin, which is considered an acute phase protein and has complex functions in an inflammatory cascade (16,17).

Procalcitonin (PCT) is a hormone precursor released by thyroid parafollicular C cells and is involved in maintaining calcium homeostasis in the body. Inflammatory stimuli, primarily those of bacterial origin, cause an increase in inflammatory levels. In the context of bacterial infections, it is frequently regarded as an acute phase reactant (18). Differentiating between bacterial and viral infections can be of utmost importance, as well as other non-infectious causes of systemic inflammation (19,20).

D-dimer is a substance that forms when a blood clot breaks down through fibrinolysis (21). The name D-dimer comes from the two D fragments of the fibrin protein that combine to form a protein dimer. These levels are used as biomarkers to predict the occurrence of a blood disorder called disseminated intravascular coagulation, particularly in coagulation disorders associated with COVID-19 infection (22). Polyunsaturated fatty acid oxidation leads to the formation of malondialdehyde (MDA), which induces stress in cells. Hence, MDA is used as a biomarker to determine the degree of oxidative stress in an organism (23). Myeloperoxidase (MPO) is most abundantly expressed in neutrophil radical granulocytes, and it can cause some oxygen to carry out their antimicrobial activity, but these radicals may also cause oxidative damage in host tissue. This also shows that MPO is a potent oxidative stress marker (24). Superoxide dismutase (SOD) is an essential enzyme that facilitates the conversion of superoxide (O_2) radicals into ordinary molecular oxygen and hydrogen peroxide. This process is vital for protecting living cells exposed to oxygen radicals by acting as an antioxidant defense mechanism (25). The enzyme family with peroxidase activity is known as glutathione peroxidase (Gpx), and its primary biological function is to safeguard the organism against oxidative harm by transforming lipid hydroperoxides to their corresponding alcohols and reducing free hydrogen peroxide to water (26). Thiols, including cysteinylglycine, homocysteine, and cysteine, have various roles in cellular functions, such as regulating; apoptosis, enzyme activity, the immune response, protein function, and mechanisms of cellular signal transduction. Thiols can also react with oxidants, undergo oxidation reactions, and form disulphide bonds, which can be reduced back to thiol groups. Therefore, thiols are considered as a part of the antioxidant system (27).

Inflammation is the primary immune response to injury or infection. This complex process requires interactions among different inflammatory, oxidative, and antioxidative

mechanisms. The impact of inflammatory markers on COVID-19 remains a subject of controversy despite considerable research. However, the association of inflammatory markers with the severity of COVID-19 was identified by a meta-analysis (28). Therefore, we aimed to determine the levels of the same markers, including CRP, ferritin, PCT, D-dimer, MDA, MPO, Gpx, SOD, and native thiols, to evaluate a possible interplay with disease severity in patients with COVID-19. These results may determine the severity and treatment options of COVID-19, especially regarding the cysteine mechanism.

METHODS

This prospective case-control study was conducted at the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, between 2020 and September 2022 with the approval of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2020-12-24, date: 08.06.2020). All participants signed written informed consent forms. A total of 125 patients were included in the study with 95% power analysis and 0.05 error level, and the G power 3.1.9.2 package program was used in the calculation.

Patient's Selection

COVID-19 infection was identified using clinical and radiological findings along with nasopharyngeal swab polymerase chain reaction positive for severe acute respiratory syndrome coronavirus 2. The research included 130 COVID-19 patients who applied to our hospital. The 130 patients with 65 in each group were assigned from a larger patient cohort. After the follow-up observation, all patients were divided into mild-moderate and severe groups according to respiratory impairment and clinical management (Table 1). A score of five or less was considered to be mild-moderate. Those who scored six or more were classified as the severe group. As a control group, we enrolled 54 healthy volunteers. Participants with a history of renal dysfunction, hypertension, cancer, otoimmun diseases, and chronic diseases such as diabetes mellitus and patients using supplemental vitamins and antioxidant drugs were excluded from the study.

Blood Sampling

Blood samples were collected from the patients on the first day of hospitalization. When measuring oxidant/antioxidant tests, it is important to pay attention to the impact of several factors such as diurnal variation, diet, and hormonal conditions. Therefore, blood sampling and routine laboratory measurements were performed while fasting in the early morning after hospitalization. After collection, the blood samples were centrifuged immediately. Serum samples were prepared by centrifugation for 10 min at 1600 g. They were stored at -80 °C until analysis. Hemolysed serum/plasma samples were discarded. At the time of admission, medical record data were used to confirm the patients' age, sex, and prior medical history.

Measurement of the Serum Oxidant/Antioxidant Parameters

The levels of serum SOD and GPx were measured using an ELISA kit that was obtained from a commercial source (Bioassay Technology Laboratory, Cat No: E0918Hu, Cat No: E3696Hu respectively, Shanghai, China). The ELISA exhibited an inter-assay variability of 10% and an intra-assay variability of 8%. SOD results are expressed as U/L, and GPx levels are expressed as ng/mL.

The serum concentration of MPO was measured using an ELISA kit that was obtained from a commercial source (Bioassay Technology Laboratory, Cat No: E0880Hu, Shanghai, China). The ELISA exhibited an inter-assay variability of 10% and an intra-assay variability of 8%. Results are expressed in ng/mL.

The serum concentration of MDA was measured using an ELISA kit that was obtained from a commercial source (Bioassay Technology Laboratory, Cat No: E1371Hu, Shanghai, China). The ELISA exhibited an inter-assay variability of 10% and an intra-assay variability of 8%. Results were expressed in nmol/mL. Commercial kits from Rel Assay Diagnostics in Gaziantep, Türkiye were used to measure native thiol levels, and the resulting values were expressed in μmol/L. After manual spectrophotometric optimization studies, CRP, uric acid, and ferritin levels were measured using an automatic analyzer (AU5800, Beckman Coulter,

Table 1. The classification criteria in the COVID-19 therapeutic trial synopsis

0	No evidence of infection
1	No limitation of activities
2	Limitation of activities
3	Hospitalized, no oxygen therapy
4	Hospitalized, oxygen by mask or nasal prongs
5	Hospitalized, non-invasive ventilation or high flow oxygen
6	Hospitalized, intubation and mechanical ventilation
7	Hospitalized, ventilation + additional organ support-pressors
8	Death

COVID-19: Coronavirus disease-19

Inc.). D-dimer was measured using an automatic analyzer (AU480, Beckman Coulter, Inc.) by the ımmunoturbidimetric method. PCT levels were measured using an automatic analyzer (DXI 800, Beckman Coulter, Inc., Fullerton, CA) using the paramagnetic particle chemiluminescent immunoassay method.

Statistical Analysis

Statistical analyses were conducted using version 21 of the SPSS software. (SPSS, Inc., Chicago, IL). The normality of the variables was examined using the Kolmogorov-Smirnov test to determine their distribution pattern. Because the measured biochemical parameters were not normally distributed, the differences between the patient and control groups were investigated using the non-parametric Mann-Whitney U test. Descriptive statistics are presented as median (minimum-maximum) for continuous variables. Statistical associations between groups and other categorical independent variables were evaluated with the χ^2 test. Because there was an age difference between groups ($p<0.001$), the significance of differential changes between the groups was tested by analysis of covariance (ANCOVA). In patients with patients (groups 1 and 2), the Spearman test was employed to compute correlation coefficients and determine their significance for variables that did not follow a normal distribution. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

A total of 130 patients infected by COVID-19 and 54 healthy control individuals (group 3) were included in this study. Among the disease contributors, 65 patients were assigned to a severe group (group 1) and 65 patients were allocated to a mild/moderate group (group 2). The male to female ratio did not significantly differ between the groups ($p>0.05$). The median age was significantly higher in both groups 1 and 2 than in group 3 ($p<0.0001$ for both). Table 1 shows the statistical analysis results of laboratory findings. According to laboratory findings that inflammation tests are important in the follow-up of the disease, the levels of CRP, ferritin, D-dimer, and PCT were significantly elevated in both groups 1 and 2, compared to group 3 ($p<0.001$ for both). There were no statistically significant differences in the MDA, MPO, SOD, and Gpx contents between groups ($p>0.05$). Furthermore, the native thiol levels were significantly lower in both groups 1 and 2 than in the other groups ($p<0.001$ for both). Moreover, we found significantly decreased native thiol levels in group 1 compared with group 2 ($p<0.001$).

The native thiol levels of all patients with COVID-19 were negatively correlated with CRP ($r=-0.362$, $p<0.001$), ferritin ($r=-0.279$, $p<0.001$), PCT ($r=-0.390$, $p<0.001$), and D-dimer ($r=-0.458$, $p<0.001$) levels (Table 2). In our study, a positive correlation was observed between inflammatory routine biochemical markers as expected [CRP levels and ferritin,

Table 2. Demographic, clinical and laboratory characteristics of study groups

	Group 1 (n=65)	Group (n=65)	Group 3 (n=54)	p[a]
Age (years)	59.9±11.6	52.0±17.1	50.2±3.0	**<0.001**
Gender (M/F)	35/30	34/31	27/27	>0.05
CRP (mg/L)	174.0 (1.2-609.6)[b,c]	17.5 (0.3-223.0)[d]	2.2 (0.3-6.2)	**<0.001**
Ferritin (ng/mL)	835.1 (20.5-9700.0)[b,c]	164.3 (4.7-1351.0)[d]	69.0 (34.0-112)	**<0.001**
PCT (ng/mL)	2.49 (0.0-1179.0)[b,c]	0.1 (0.0-3.9)[d]	0.0 (0.0-0.0)	**<0.001**
D-dimer (µg FEU/mL)	2.46 (0.1-8.0)[b,c]	0.3 (0.0-3.5)[d]	0.2 (0.1-0.4)	**<0.001**
Uric acid (mg/dL)	4.3 (0.9-13.6)	4.2 (1.6-13.8)	4.5 (2.1-7.8)	>0.05
MDA (nmol/L)	5.7 (0.7-83.9)	5.3 (1.0-84.0)	6.1 (1.6-83.9)	>0.05
MPO (ng/mL)	1.8 (0.9-32.1)	1.9 (0.9-30.3)	1.8 (0.9-33.5)	>0.05
SOD (U/L)	66.4 (4.0-1006.5)	62.0 (4.5-924.0)	72.0 (1.9-1004.6)	>0.05
GPx (ng/mL)	23.9 (10.7-192.0)	24.7 (7.0-101.0)	25.9 (1.4-99.3)	>0.05
Native thiol (µmol/L)	82.4 (4.8-387.7)[b,c]	178.5 (22.7-438.0)[d]	455.5 (245.0-757.3)	**<0.001**

Laboratory data are presented as the median and minimum-maximum values. p[a]: P-value between groups, $p<0.001$ was statistically significant
[b]Shows differences with group 1 and group 2 with $p<0.001$
[c]Shows differences with group 1 and group 2 with $p<0.001$
[d]Shows differences with group 1 and group 2 with $p<0.001$
Group 1; severe, group 2; mild/moderate according to their symptoms, group 3; control group
M: Male, F: Female, CRP: C-reactive protein, PCT: Procalcitonin, MDA: Malondialdehyde, MPO: Myeloperoxidase, SOD: Superoxide dismutase, Gpx: Glutathione peroxidase

PCT, D-dimer levels in all COVID-19 patients (r=0.637, p<0.001, r=0.788, p<0.001, r=0.542, p<0.001 respectively)]. Although we could not find any significant differences in GPx, MDA, MPO, and SOD levels between the groups (Table 2), a strong positive correlation was observed among these markers in all the patients (Table 3).

DISCUSSION

Our results revealed that severe patients with COVID-19 had higher serum CRP, ferritin, D-dimer, and PCT levels than both moderate patients and controls, in accordance with the literature findings. However, similar MDA, MPO, Gpx, and SOD levels were measured among the groups. The findings of this study indicated that serum native thiol values were lower in both severe and moderate patients with COVID-19 than in healthy controls.

The clinical course of COVID-19 depends on several factors such as cytokine storm, excessive inflammation, and low blood oxygen levels (11,12). It clearly identified the association of inflammatory markers with the severity of COVID-19 in a meta-analysis (28).

Therefore, measurement of inflammatory markers may be useful to monitor and evaluate the severity and prognosis of the disease. Serum levels of CRP, D-dimers, ferritin, and cardiac troponins are used for risk stratification in hospitalized patients (8). It has been reported that inflammation and coagulation are responsible for mortality in this population. An increased circulating level of inflammatory markers, such as CRP, is characterized during the development of a "cytokine storm". and indicates a strong correlation between prognosis and disease severity in COVID-19 patients (13-15,29-31). Our CRP results are consistent with the literature findings. The inflammatory response is not fully understood, but the innate immune response may contribute to the severity of this disease (31).

Many studies have reported that COVID-19 infection may affect iron metabolism. Higher concentrations of serum ferritin in severe cases were found to be associated with poor prognosis versus milder cases (32). COVID-19 is one of the rare "hyperferritinemic" diseases characterized by increased ferritin levels and cytokine storm (33). Similar to these study results, we found higher ferritin levels in a patient with severe disease when compared with other groups. This could result from the potential impact of impaired iron metabolism or may be increased as acute phase reactants.

According to a meta-analysis, PCT levels are higher than CRP levels in distinguishing bacterial infections from both viral infections and non-infectious causes of systemic inflammation (20). This distinguishing feature makes PCT a valuable diagnostic marker. On the other hand, viruses can increase serum PCT levels. Especially during coronavirus and influenza A, infections had higher PCT levels than the other studied ones (34). In addition to these findings, elevated PCT levels are reported in patients with COVID-19, and higher levels are positively associated with disease severity (7,35). In a meta-analysis, it was reported that ~5-fold increased PCT levels are related to a higher risk of severe disease. In addition, a progressive increase in PCT levels may predict a worse prognosis (36). Therefore, serial PCT measurements could be important to predict the evolution toward a more severe form of COVID-19. In our study, we found higher PCT levels in both severe and mild/moderate patients with COVID-19 when compared with control patients, consistent with the literature (7,35,37). The underlying mechanism of increasing PCT levels and disease severity in patients with COVID-19 is not fully understood.

Table 3. Correlation analysis between characteristics and biochemical parameters in patients with COVID-19

Variables	Ferritin	Native thiol	PCT	D-dimer	GPx	MDA	MPO	SOD	Age
C-reactive protein (mg/L)	**0.637****	**-0.362****	**0.788****	**0.542****	**-0.206***	**-0.174***	**-0.231****	-0.172	**0.194***
Ferritin (ng/mL)	-	**-0.279****	**0.681****	**0.446****	-0.103	-0.084	-0.49	-0.035	0.151
Native thiol (µmol/L)	-	-	**-0.390****	**-0.458****	0.062	0.090	0.001	-0.030	0.102
Procalcitonin (ng/mL)	-	-	-	**0.681****	-0.087	-0.048	-0.072	-0.080	**0.206***
D-dimer (µg FEU/mL)	-	-	-	-	-0.064	-0.038	-0.011	-0.096	0.102
Glutathione peroxidase (ng/mL)	-	-	-	-	-	**0.843****	**0.860****	**0.829****	**-0.252****
Malondialdehyde (nmol/L)	-	-	-	-	-	-	**0.883****	**0.886****	-0.901
Myeloperoxidase (ng/mL)	-	-	-	-	-	-	-	**0.882****	**-0.198***
Superoxide dismutase (U/L)	-	-	-	-	-	-	-	-	**-0.180***

*p<0.05, **p<0.001
PCT: Procalcitonin, MDA: Malondialdehyde, MPO: Myeloperoxidase, SOD: Superoxide dismutase, Gpx: Glutathione peroxidase, COVID-19: Coronavirus disease-19

It could be associated with concomitant bacterial infection during moderate disease because the co-infection rate is similar to the rate of increased PCT levels in this population. However, especially in severe and critical patients, the co-infection rate is different from the PCT increasement (37).

Another test increasing during COVID-19 is D-dimer, which has demonstrated a poor prognosis for coagulopathy, especially in severe patients, similar to our study result (4,6,38,39). D-dimer indicates both the activation of coagulation and fibrinolytic system. The D-dimer consists of two D fragments of fibrin and shows a demolished fibrin (21). Several mechanisms, such as inflammatory response and endothelial dysfunction, may increase D-dimer levels in patients with COVID-19. In addition, hypoxia, age, the existence of concomitant disease, and long-term hospitalization may result in coagulation disorders in this population (22). In the present study, we found significantly higher D-dimer levels in the severe group than in the mild/moderate and control groups.

Oxidative stress is an important and possible mechanism in COVID-19 pathogenesis (40). Viral replication results in oxidative damage, which is related to the severity of the infection. Moreover, antioxidants may prevent the virus from replicating efficiently, and milder symptoms are observed in clinical practice (41). Therefore, an understanding of the molecular mechanisms of oxidative stress in COVID-19 is required to improve therapies (42). Although clinical evidence suggests that the redox profile could be an important factor in the severity of COVID-19 pathogenesis, there is limited detailed descriptive data on oxidative stress during the progression of COVID-19 (42,43). Several studies have suggested that the overproduction of reactive oxygen species and decreased antioxidant function could be important in regulating COVID-19 pathogenesis (42-44). On the contrary, it was recently reported similar oxidant production and antioxidant capacity during disease progression. Gadotti et al. (45) performed this study only in patients with COVID-19 without control individuals. Our study also includes controls. In our study, patients with COVID-19 (both severe and moderate) exhibited counterpart MDA, MPO, SOD, and Gpx levels compared with those of control individuals. These conflicting results between studies may be related to the measurement methodology of biochemical markers, sampling time, and number of cases investigated.

In our study, a significant decrease in native thiol levels was observed in severe COVID-19 patients compared with the moderate and control groups. The plasma thiol pool primarily comprises albumin and protein thiols, as well as low-molecular-weight thiols such as cysteine, cysteinyl glycine, glutathione, homocysteine, and gamma-glutamylcysteine, albeit in smaller amounts (46). Thiols are the major component of the total antioxidant mechanisms and defense against oxidative stress (47-49). Recently, Kalem et al. (50) reported that both native and total thiol levels in COVID-19 patients were lower than those in the control group. They also postulated that the native thiol level is an indicator of the presence of the disease and a predictor of disease severity, similar to our study results. We found a statistically significant negative correlation between native thiol and disease severity markers, such as CRP, ferritin, PCT, and D-dimer, in patients with COVID-19. It has been speculated that native thiols could play an important role in the elimination of increased production of ROS, and thus levels of this marker may decrease. In other words, the lower native thiol levels may be due to their conversion to disulphides under inflammatory conditions in our study. However, we did not measure the disulphide levels in our study participants. Kalem et al. (50) also reported higher disulphide levels in patients with mild to moderate COVID-19 than in controls. Interestingly, similar disulphide levels between severe patients with COVID-19 and controls have been reported. The exact mechanism behind why disulphide levels increased in mild patients compared with the control group but not in severe ones is unclear. Therefore, more research is necessary on this topic. It has been shown in many animal and human studies that N-acetylcysteine (NAC) is beneficial for treating COVID 19 (51-55). We believe that understanding the relationship between thiol and COVID-19 can also provide information on whether NAC treatment will be effective or not via the cysteine mechanisms. However, more extensive studies are required on this subject. Our study limitations are that we could not measure iron and disulphide levels in our study participants due to economical problems with small study groups.

CONCLUSION

In severe COVID-19 cases, while CRP, ferritin, D-dimer and PCT increase, native thiol levels decrease in line with the literature results. We believe that the thiol mechanism should be investigated, especially in larger study groups, to develop the prognosis and treatment protocols of these COVID-19 patients.

ETHICS

Ethics Committee Approval: This prospective case-control study was conducted at the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and

Research Hospital, between 2020 and September 2022 with the approval of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2020-12-24, date: 08.06.2020).

Informed Consent: All participants signed written informed consent forms.

Authorship Contributions

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

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

Financial Disclosure: The study is supported by the Scientific Research Projects Coordinatorship of the University of Health Sciences, Türkiye (Project no: 2020/063).

REFERENCES

1. Ayres JS. A metabolic handbook for the COVID-19 pandemic. Nat Metab 2020;2:572-85.
2. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol 2020;215:108427.
3. Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G. Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. Cell Stress 2020;4:66-75.
4. 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.
5. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020;58:1021-8.
6. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol 2020;146:89-100.
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
8. Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. Int J Infect Dis 2020;95:304-7.
9. Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, et al. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:E005.
10. Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol 2020;92:791-6.
11. Fara A, Mitrev Z, Rosalia RA, Assas BM. Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. Open Biol 2020;10:200160.
12. Lazzaroni MG, Piantoni S, Masneri S, Garrafa E, Martini G, Tincani A, et al. Coagulation dysfunction in COVID-19: The interplay between inflammation, viral infection and the coagulation system. Blood Rev 2021;46:100745.
13. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111:1805-12.
14. Mooiweer E, Luijk B, Bonten MJ, Ekkelenkamp MB. C-Reactive protein levels but not CRP dynamics predict mortality in patients with pneumococcal pneumonia. J Infect 2011;62:314-6.
15. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846-8.
16. Taneri PE, Gómez-Ochoa SA, Llanaj E, Raguindin PF, Rojas LZ, Roa-Díaz ZM, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. Eur J Epidemiol 2020;35:763-73.
17. Reif DW. Ferritin as a source of iron for oxidative damage. Free Radic Biol Med 1992;12:417-27.
18. Lippi G, Cervellin G. Procalcitonin for diagnosing and monitoring bacterial infections: for or against? Clin Chem Lab Med 2018;56:1193-5.
19. Le Bel J, Hausfater P, Chenevier-Gobeaux C, Blanc FX, Benjoar M, Ficko C, et al. Diagnostic accuracy of C-reactive protein and procalcitonin in suspected community-acquired pneumonia adults visiting emergency department and having a systematic thoracic CT scan. Crit Care 2015;19:366.
20. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis 2004;39:206-17.
21. Gaffney PJ. Breakdown products of fibrin and fibrinogen: molecular mechanisms and clinical implications. J Clin Pathol Suppl (R Coll Pathol) 1980;14:10-7.
22. 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.
23. Del Rio D, Stewart AJ, Pellegrini N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. Nutr Metab Cardiovasc Dis 2005;15:316-28.
24. Abu-Soud HM, Maitra D, Shaeib F, Khan SN, Byun J, Abdulhamid I, et al. Disruption of heme-peptide covalent cross-linking in mammalian peroxidases by hypochlorous acid. J Inorg Biochem 2014;140:245-54.
25. Hayyan M, Hashim MA, AlNashef IM. Superoxide Ion: Generation and Chemical Implications. Chem Rev 2016;116:3029-85.
26. Muthukumar K, Nachiappan V. Cadmium-induced oxidative stress in Saccharomyces cerevisiae. Indian J Biochem Biophys 2010;47:383-7.
27. Biswas S, Chida AS, Rahman I. Redox modifications of protein-thiols: emerging roles in cell signaling. Biochem Pharmacol 2006;71:551-64.
28. Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis 2020;96:467-74.
29. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol 2020;127:104370.
30. D'Alessandro A, Thomas T, Dzieciatkowska M, Hill RC, Francis RO, Hudson KE, et al. Serum Proteomics in COVID-19 Patients: Altered Coagulation and Complement Status as a Function of IL-6 Level. J Proteome Res 2020;19:4417-27.
31. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75:1730-41.
32. Bennett TD, Hayward KN, Farris RW, Ringold S, Wallace CA, Brogan TV. Very high serum ferritin levels are associated with

increased mortality and critical care in pediatric patients. Pediatr Crit Care Med 2011;12:e233-6.
33. Colafrancesco S, Alessandri C, Conti F, Priori R. COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome? Autoimmun Rev 2020;19:102573.
34. Lee CC, Chang JC, Mao XW, Hsu WT, Chen SY, Chen YC, et al. Combining Procalcitonin and Rapid Multiplex Respiratory Virus Testing for Antibiotic Stewardship in Older Adult Patients With Severe Acute Respiratory Infection. J Am Med Dir Assoc 2020;21:62-7.
35. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.
36. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta 2020;505:190-1.
37. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. Int J Antimicrob Agents 2020;56:106051.
38. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094-9.
39. Fogarty H, Townsend L, Ni Cheallaigh C, Bergin C, Martin-Loeches I, Browne P, et al. COVID19 coagulopathy in Caucasian patients. Br J Haematol 2020;189:1044-9.
40. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355-62.
41. Polonikov A. Endogenous Deficiency of Glutathione as the Most Likely Cause of Serious Manifestations and Death in COVID-19 Patients. ACS Infect Dis 2020;6:1558-62.
42. Beltrán-García J, Osca-Verdegal R, Pallardó FV, Ferreres J, Rodríguez M, Mulet S, et al. Oxidative Stress and Inflammation in COVID-19-Associated Sepsis: The Potential Role of Anti-Oxidant Therapy in Avoiding Disease Progression. Antioxidants (Basel) 2020;9:936.
43. Delgado-Roche L, Mesta F. Oxidative Stress as Key Player in Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Infection. Arch Med Res 2020;51:384-7.
44. Fakhri S, Nouri Z, Moradi SZ, Farzaei MH. Astaxanthin, COVID-19 and immune response: Focus on oxidative stress, apoptosis and autophagy. Phytother Res 2020;34:2790-2.
45. Gadotti AC, Lipinski AL, Vasconcellos FT, Marqueze LF, Cunha EB, Campos AC, et al. Susceptibility of the patients infected with Sars-Cov2 to oxidative stress and possible interplay with severity of the disease. Free Radic Biol Med 2021;165:184-90.
46. Turell L, Radi R, Alvarez B. The thiol pool in human plasma: the central contribution of albumin to redox processes. Free Radic Biol Med 2013;65:244-53.
47. Chianeh YR, Prabhu K. Protein thiols as an indicator of oxidative stress. Arch Med Rev J 2014;23:443-56.
48. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem 2014;47:326-32.
49. Lavillette D, Barbouche R, Yao Y, Boson B, Cosset FL, Jones IM, et al. Significant redox insensitivity of the functions of the SARS-CoV spike glycoprotein: comparison with HIV envelope. J Biol Chem 2006;281:9200-4.
50. Kalem AK, Kayaaslan B, Neselioglu S, Eser F, Hasanoglu İ, Aypak A, et al. A useful and sensitive marker in the prediction of COVID-19 and disease severity: Thiol. Free Radic Biol Med 2021;166:11-7.
51. Davreux CJ, Soric I, Nathens AB, Watson RW, McGilvray ID, Suntres ZE, et al. N-acetyl cysteine attenuates acute lung injury in the rat. Shock 1997;8:432-8.
52. Ungheri D, Pisani C, Sanson G, Bertani A, Schioppacassi G, Delgado R, et al. Protective effect of n-acetylcysteine in a model of influenza infection in mice. Int J Immunopathol Pharmacol 2000;13:123-8.
53. Andreou A, Trantza S, Filippou D, Sipsas N, Tsiodras S. COVID-19: The Potential Role of Copper and N-acetylcysteine (NAC) in a Combination of Candidate Antiviral Treatments Against SARS-CoV-2. In Vivo 2020;34(3 Suppl):1567-88.
54. Horowitz RI, Freeman PR, Bruzzese J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: a report of 2 cases. Respir Med Case Rep 2020;30:101063.
55. Ibrahim H, Perl A, Smith D, Lewis T, Kon Z, Goldenberg R, et al. Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine. Clin Immunol 2020;219:108544.

Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:397-411
DOI: 10.4274/BMJ.galenos.2023.2022.12-14

Research

Evaluation of Genital Hiatus and Perineal Body Measurement in Women in Turkish Society, According to Recurrent Vaginitis and Vaginal Flatus

Türk Toplumunda Kadınlarda Genital Hiatus ve Perineal Body Boyutlarının Değerlendirilmesi ve Tekrarlayan Vajinit ve Vajinal Flatus ile İlişkisi

Halide Efendi, Keziban Doğan

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

ABSTRACT

Objective: In our study, we aimed to determine the mean values of genital hiatus (GH) and perineal body (PB) measurements in the Turkish population to investigate the factors affecting the measurements and the effect of the values on the frequency of recurrent vaginitis and vaginal flatus.

Methods: Our study was conducted by taking GH and PB measurements in 405 women between the ages of 18 and 45 years who had never given birth and had a single birth. Body mass index (BMI), diseases, surgeries, duration of active coitus, recurrent vaginitis, and vaginal flatus symptoms were assessed.

Results: In all subjects, the mean GH value was 23.8 mm and the mean PB value was 31.1 mm. The GH values of the subjects in the vaginal delivery (NSD) group were significantly higher than those in the never delivered (nullipar) and cesarean delivery (CS) groups (p=0.016, p=0.021; p<0.05). Recurrent vaginitis was significantly lower in nulliparous patients (p=0.003; p<0.01). There was a statistically significant positive correlation between GH and BMI measurements, mediolateral episiotomy, and age. A statistically significant positive correlation was observed between PB and BMI measurements and active coitus duration. According to the history of recurrent vaginitis and vaginal flatus, GH and PB measurements of the subjects did not show a statistically significant difference (p>0.05).

Conclusion: The mean GH value was 23.8 mm and the average PB length was 31.1 mm in Turkish women. It was found that GH enlarged due to single vaginal delivery, mediolateral episiotomy, age and weight, and recurrent vaginitis was less common in nulliparous patients. According to these results, even a single delivery causes changes in the pelvic floor. Increased GH levels may disrupt the defense mechanisms of the vagina and increase the risk of infection. We believe that it is important to increase primiparous births without performing episiotomy and weight control.

Keywords: Genital hiatus, perineal body, recurrent vaginitis, vaginal flatus

ÖZ

Amaç: Çalışmamızda Türk toplumunda genital hiatus (GH) ve perineal body (PB) ölçümlerinin orta değerlerini bulmayı, ölçümlerin etkilendiği faktörleri ve değerlerin tekrarlayan vajinit, vajinal gaz sıklığına etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmamız 18-45 yaş arası hiç doğum yapmamış ve tek doğum yapmış 405 kadında GH ve PB ölçümleri alınarak yapılmıştır. Bu hastalarda vücut kitle indeksi (VKİ), hastalıklar, geçirilen cerrahiler, aktif koit süresi, tekrarlayan vajinit ve vajinal gaz semptomları sorgulanmıştır.

Bulgular: Tüm olgularda GH ortalama değer 23,84 mm, PB ortalama değer 31,13 mm bulundu. Vajinal doğum yapan (NSD) grubundaki olguların GH değerleri, hiç doğum yapmamış (nullipar) ve sezeryan ile doğum yapmış (CS) grubundakilerden anlamlı yüksektir (p=0,016, p=0,021; p<0,05). Nullipar olgularda tekrarlayan vajinit sıklığı anlamlı olarak daha düşük tespit edildi (p=0,003; p<0,01). Olguların GH ile VKİ ölçümleri, mediolateral epizyotomi ve yaş arasında pozitif yönlü istatistiksel anlamlı ilişki saptanmıştır. Olguların PB ile VKİ ölçümleri ve aktif koit süreleri arasında pozitif yönlü istatistiksel anlamlı ilişki saptanmıştır. Tekrarlayan vajinit ve vajinal gaz öyküsüne göre olguların GH ve PB ölçümleri, istatistiksel olarak anlamlı farklılık göstermemektedir (p>0,05).

Address for Correspondence: Halide Efendi, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Türkiye
Phone: +994103248401 E-mail: xalide.efendi@mail.ru ORCID ID: orcid.org/0000-0003-2245-9819

Cite as: Efendi H, Doğan K. Evaluation of Genital Hiatus and Perineal Body Measurement in Women in Turkish Society, According to Recurrent Vaginitis and Vaginal Flatus. Med J Bakirkoy 2023;19:397-411

Received: 03.01.2023
Accepted: 18.12.2023

Sonuç: Türk kadınlarında ortalama GH değeri 23,8 mm ve ortalama PB uzunluğu 31,1 mm idi. Tek vajinal doğum, mediolateral epizyotomi, yaş ve kiloya bağlı olarak GH genişlediği ve nullipar kadınlarda tekrarlayan vajinitin daha az olduğu saptandı. Bu sonuçlara göre tek bir doğum bile pelvik tabanda değişikliklere neden olmaktadır. Artan GH vajinanın savunma mekanizmalarını bozabilir ve enfeksiyon riskini artırabilir. Bu veriler ışığında kilo kontrolünün ve epizyotomisiz primipar doğumların artırılmasının önemli olduğuna inanıyoruz.

Anahtar Kelimeler: Genital hiatus, perineal body, tekrarlayan vajinit, vajinal flatus

INTRODUCTION

Genital hiatus (GH) is the anatomical structure connecting the vagina and external genital organs. The perineal body (PB) is located at the center of the perineum and divides the perineum into urogenital and anogenital triangles. Interlocking fibers of the superficial transverse perineal muscles, posterior fibers of the bulbocavernosus muscles, and fibers of the external anal sphincter form the PB structure (1). GH is characterized as the point between the center of the external urethral meatus and the posterior edge of the hymen, and PB is identified as the distance between the posterior edge of the hymen and the midpoint of anus (2). GH and PB measurements have been defined with respect to the terminology of female pelvic organ prolapse (POP) by the joint publication of the International Urogynecological Association and International Continence Society in the Pelvic Organ Prolapse Rating system (POP-Q) (3). This standardization is ensured with an attempt to avoid variations among physicians.

Vaginitis, inflammation of the vagina, can be observed on disruption of the vaginal ecosystem, producing substances such as lactic acid and hydrogen peroxide that inhibit the growth of bacteria, not belonging in the vaginal microbiota. The most common symptoms are itching, burning sensation, abnormal odor, and discharge. However, most patients are asymptomatic and do not require treatment (4,5). Based on the causative organism, there are three main types of vaginitis: bacterial vaginosis, candidiasis, and trichomaniasis (6).

Vaginal flatulence is the state of gas emission from the vagina in women. It was established as a symptom of pelvic floor dysfunction by the International Continence Society and International Urogynecological Association in 2017, but it is also a complaint that can be encountered with changes occurring in the normal vaginal flora during menstruation (7). Experience of vaginal flatus is common amongst women. It has not been emphasized mainly because it is not considered as a life-threatening condition and not questioned in detail (8). Its frequency in women giving birth increases up to 71% and negatively impacts the quality of life (9,10).

Vaginal infection and vaginal flatus are non- life-threatening but annoying health problems. On review of the literature, although the mean values of PB and GH in women without prolapse are not known precisely, no study has evaluated the average measurements in any ethnic group. In addition, the vagina may be exposed to external factors due to the enlargement of the GH and shortening of the PB. Therefore, the tendency to vaginal infections may increase and vaginal flatus may increase secondary to the relaxation of the vaginal muscles and chronic infections. In our study, we aimed to demonstrate the mean GH and PB values in nulliparous women of Turkish ethnicity and in those who had one vaginal or abdominal delivery, as well as assess their association with descriptive characteristics such as body mass index (BMI), vaginitis, and vaginal flatulence.

METHODS

The study was designed as a prospective cross-sectional study and upon receipt of the necessary ethics committee approval, it was conducted on women aged 18-45 with Turkish ethnic origin who presented to the Department of Obstetrics and Gynecology, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital between the dates of February 15, 2021 and February 15, 2022 (University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee- decision no: 2021-03-19, date: 01.02.2021). Informed consent was obtained from the patients. GH and PB measurements were taken using a digital caliper. Age, height, weight, types of delivery, active coitus duration, vaginal flatulence, and vaginitis symptoms were determined. A total of 405 patients meeting the criteria were included in the study and were analyzed in three groups. The first group consisted of nulliparous participants who had never given birth, the second group had individuals with a history of one vaginal delivery, and those with a history of one cesarean section formed the third group. Information related to age, height, weight, BMI [BMI-weight(kg)/height^2(m^2)], types of delivery, active coitus time, vaginal flatus, and vaginitis symptoms for the patients in all three groups were documented. Patients with a history of vaginitis more than twice a year were defined as frequent, and those with two or fewer episodes were defined as rare. Exclusion criteria of the study were as follows: pregnant women, those who underwent vaginal surgery, patients of non-Turkish ethnicity, patients under the age of 18 and aged

above 45 years, history of giving birth to an infant weighing over 4000 g, history of assisted delivery (using vacuum, forceps, etc.), and those who had 2 or more births.

GH and PB lengths of all patients included in the study were measured in the lithotomy position using a digital caliper while performing the Valsalva maneuver. The measurement unit of the digital caliper was set to millimeters. Measurements were taken by a single researcher (Dr. Halide Efendi). The lengths of GH and PB were compared in patients who had never given birth, those with a history of a single vaginal delivery, and those with a previous cesarean section, and the average of GH and PB values was calculated for all participants. GH and PB measurements were analyzed with respect to BMI, duration of coitus, frequency of vaginitis, and incidence of vaginal flatulence. Experience of vaginitis more than twice a year was noted as frequent, and occurrence of the condition twice or less was defined as rare.

Statistical Analysis

Regarding the performance of power analysis, the required number of cases for a power of 80% was found to be 400. The Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the study data. The conformity of quantitative data to the normal distribution was tested using the Shapiro-Wilk test and graphical examinations. One-Way analysis of variance and Bonferroni corrected binary evaluations were performed for comparisons of normally distributed quantitative variables between more than two groups. Kruskal-Wallis and Dunn-Bonferroni tests were performed to assess quantitative variables with nonnormal distribution between more than two groups. The Fisher-Freeman-Halton exact test was used to evaluate qualitative data. Spearman correlation analysis of relationships was performed with regard to quantitative variables. Statistical significance was accepted as a p-value of 0.05.

RESULTS

In the study, the ages of the patients ranged from 18 to 45 years; the mean age was 29.94±7.17. A total of n=405 women were included. On examination of the groups, 63% (n=255) were nulliparous, 15.8% (n=64) had one vaginal delivery (NSD), and 21.2% (n=86) underwent one cesarean section (CS). Although vaginitis was not identified in 75.3% of the cases, rare vaginitis was detected in 8.9% (n=36) and recurrent vaginitis was observed in 15.8% (n=64). There was also no history of vaginal flatulence in 62.5% (n=253) of women, whereas it was rare in 28.4% (n=115) and common in 9.1% (n=37). The active coitus periods of the cases varied from 0.8 to 28 years; the mean duration was 6.24±6.02 years. In addition, the average GH value of all cases was 23,843 mm, and the mean PB length was 31,134 mm.

As shown in Table 1, a statistically significant difference was demonstrated between the ages and BMI of

Table 1. Comparison of descriptive characteristics by groups

		Groups			p-value
		Nulliparous (n=255)	NSD (n=64)	CS (n=86)	
Age (year)	Mean ± SD	27.83±6.59*	33.50±7.43	33.56±6.16	[a]**0.001****
	Median (min-max)	27 (18-45)	33.5 (20-45)	33 (19-45)	
BMI	Mean ± SD	24.63±5.09*	26.65±5.54	27.03±6.24	[c]**0.001****
	Median (min-max)	21.1 (15.8-40.6)	25.2 (17.4-45)	26.1 (16.6-45.7)	
History of recurrent vaginitis (year)	No	206 (80.8)*	39 (60.9)	60 (69.8)	[b]**0.003****
	Rare	19 (7.5)	11 (17.2)	6 (7.0)	
	Frequent	30 (11.8)	14 (21.9)	20 (23.3)	
Vaginal flatus	No	169 (66.3)	32 (50.0)	52 (60.5)	[b]**0.117**
	Rare	66 (25.9)	22 (34.4)	27 (31.4)	
	Frequent	20 (7.8)	10 (15.6)	7 (8.1)	
Active coit time (year)	Mean ± SD	3.73±4.14*	10.68±7.17	10.47±5.60	[a]**0.001****
	Median (min-max)	2.5 (0.1-28)	9 (0.7-26)	9 (2-24)	

[a]Kruskal-Wallis test and Dunn Bonferonni test, [b]Fisher-Freeman-Halton test, [c]One-Way ANOVA test and Dunn Bonferroni test, **p<0.01 P0: Nulliparous, NSD: Vaginal delivery, CS: Cesarean delivery, BMI: Body mass index, SD: Standard deviation, min-max: Minimum-maximum

participants with respect to the groups (p=0.001; p<0.01). Based on the results of pairwise comparisons carried out to determine the source of the difference, the ages and BMI of women in the nulliparous group were notably less than those in the NSD and CS groups (p=0.001; p=0.001; p<0.01). A statistically meaningful variance was detected among subjects in relation to history of recurrent vaginitis according to the groups (p=0.003; p<0.01). The frequency of recurrent vaginitis in nulliparous cases was significantly lower than that in the NSD and CS cohorts. The incidence of recurrent vaginitis was found to be higher in the NSD group than in the nulliparous and CS groups. With regard to the active coitus times of participants, a statistically significant difference was identified between the groups (p=0.001; p<0.01); active coitus periods of nulliparous cases were remarkably lower than those in the NSD and CS groups (p=0.001; p=0.001; p<0.01).

On review of the groups, there was no statistically meaningful difference revealed regarding the experience of vaginal flatulence among the cases (p>0.05).

As shown in Table 2, a statistically notable difference was observed between the GH measurements of cases according to the groups (p=0.003; p<0.01). On conduction of pairwise comparisons determining the source of difference, the GH values of participants in the NSD group were remarkably higher than those in the nulliparous and CS groups (p=0.016, p=0.021; p<0.05). There was no statistically significant variance between PB lengths (p>0.05).

On evaluation of the Spearman correlation test between GH, PB lengths and BMI, mediolateral episiotomy, midline episiotomy, and active coitus times, a positive statistically weak correlation was established between GH and BMI measurements, as presented in Table 3 (r=0.380; p=0.001; p<0.01). There was also a positive, yet statistically very weak relationship between GH and mediolateral episiotomy measurements (with higher GH value, mediolateral episiotomy length increased) (r=0.174; p=0.001; p<0.01). No statistically significant association was demonstrated between GH measurements and the ages of participants, midline episiotomy, and active coitus durations (p>0.05). Whilst there was a statistically very weak positive correlation between the ages of patients and PB lengths (with rising age, PB increased) (r=0.141; p=0.004; p<0.01), a positive relationship with a statistically low level was identified regarding BMI measurements (increasing PB associated with higher BMI values) (r=0.346; p=0.001; p<0.01). A positive, yet statistically very weak linear correlation existed between PB values and active coitus times (as PB increased, active coitus periods lengthened) (r=0.183; p=0.001; p<0.01). On the other hand, no statistically significant relationship was revealed between PB measurements and mediolateral episiotomy or midline episiotomy (p>0.05).

As listed in Table 4, the GH and PB measurements of cases did not show a statistically significant difference with regard to the history of recurrent vaginitis and vaginal flatus (p>0.05).

DISCUSSION

In our study, we identified the mean value of GH as 23.8 mm and that of PB as 31.1 mm in our measurements of women of Turkish ethnicity. On review of the literature, we could not detect a similar study conducted on Turkish women, yet as the mean PB measurement was 3.7±0.9 cm in Caucasian women, it was revealed as 3.6±0.9 cm in women of Asian origin. With these results, it was observed that the mean PB lengths detected in Caucasian and Asian women were longer than that of Turkish individuals (11). Additionally, PB measurements were made in the early and late stages of labor in Vietnamese pregnant women, and the average PB value was found to be 3.4 cm in the early stage and 4.3 cm in the second stage (12). With respect to a study conducted on Chinese women, PB lengths were measured in the first stage of labor, at the beginning and end of the second stage and the values were found to be 38.8 mm, 49.4 mm and 59.4 mm, and PB measurement lengthened with approaching

Table 2. Comparison of GH, PB measurements by groups

		Groups			p-value
		Nulliparous (n=255)	NSD (n=64)	CS (n=86)	
GH	Mean ± SD	23.45±5.78	26.15±7.06*	23.28±5.45	c**0.003****
	Median (min-max)	23 (10.1-49)	25.7 (11.2-47.2)	22.1 (10.8-43.7)	
PB	Mean ± SD	31.05±6.09	31.65±7.20	31.02±5.04	c**0.761**
	Median (min-max)	30.9 (0-50.8)	30.7 (18-51)	30.9 (20.2-45.8)	

cOne-Way ANOVA test and Dunn Bonferroni test, **p<0,01, bFisher-Freeman-Halton test, NSD: Vaginal delivery, CS: Cesarean delivery, GH: Genital hiatus, PB: Perineal body, SD: Standard deviation, min-max: Minimum-maximum

labor due to the pressure related to fetal head engagement (13). However, our study was not conducted on pregnant women.

Based on our results, we determined that GH was larger in women with a history of vaginal births than in nulliparous participants or those delivering via cesarean section. Similarly, in another study conducted on 1,224 patients, GH was found to be greater in the group who delivered vaginally in contrast to those with a history of cesarean section (14). These data support the notion that vaginal birth creates permanent changes in the vaginal tissue and GH. In comparison, no difference was identified related to PB measurements of nulliparous and primiparas women or with regard to mode of delivery among primiparas patients. We attributed these results to the fact that first births were generally at a young age, and it was easier for the perineal muscles to return to their prenatal shape. We also concluded that perineal deformity might have developed less frequently in women with a history of one single delivery. Likewise, in a study performed on 112 cases, no significant difference was noted regarding PB measurements of participants in the vaginal birth and cesarean section groups 6 months post birth (15). However, more extensive studies are required on this matter, especially including multiparous.

Although there was a weak correlation, we found that GH measurement increased because of the increase in BMI and the presence of mediolateral episiotomy. In addition, PB was measured longer in parallel with the increase in BMI, age, and coit duration. Similarly, in a study conducted on 1,043 women, obesity and POP-Q were evaluated, and a positive association was found between obesity and the sum of PB and GH (16). Contrary to our findings, in a study conducted with Korean women, no relationship was established between obesity and POP-Q. In this study, GH and PB were not assessed separately (17). In a study conducted on 549 women, patients with and without mediolateral episiotomy were examined , and GH and PB measurements were shown to be short in the group with episiotomy (18). We believe that further studies are needed with larger patient cohorts because the number of participants who underwent midline episiotomy was significantly lower in our study and the cases had only one delivery.

In a study conducted to determine the relationship between GH and PB lengths and POP, both GH and PB measurements showed a weak correlation with age. However, unlike our study, 90% of the patients in this study were multiparous women (19). In a retrospective study aiming to identify the independent risk factors of POP, evaluating 244 cases with prolapse and 314 participants without prolapse, GH

Table 3. The relationship between GH, PB lengths and BMI, mediolateral episiotomy, midline episiotomy and active coitus periods

		GH	PB
Age (year)	r	0.029	0.141
	p	0.567	0.004**
BMI	r	0.380	0.346
	p	0.001**	0.001**
Mediolateral episiotomy	r	0.174	0.023
	p	0.001**	0.643
Midline episiotomy	r	0.044	0.059
	p	0.379	0.235
Active coit time (year)	r	0.060	0.183
	p	0.231	0.001**

r: Spearman correlation test, **p<0.01, GH: Genital hiatus, PB: Perineal body, BMI: Body mass index

Table 4. Comparison of GH, PB lengths with vaginitis and vaginal flatulence symptoms

		GH			PB		
		Mean ± SD	Median (min-max)	p	Mean ± SD	Median (min-max)	p
History of recurrent vaginitis	No	23.81±5.98	23 (10.8-49)	c**0.647**	31.42±6.22	31.1 (0-51)	c**0.079**
	Rare	24.68±6.79	24.5 (13.7-47.2)		29.04±5.38	28.7 (19-42.5)	
	Frequent	23.54±5.70	24 (10.1-35.6)		30.93±5.51	31.2 (18.8-44.1)	
Vaginal flatus	No	23.64±6.25	22.9 (11.2-49)	c**0.304**	31.39±6.12	31.4 (0-51)	c**0.420**
	Rare	23.83±5.60	23.5 (10.1-43.2)		30.50±5.97	29.9 (18-47)	
	Frequent	25.27±5.42	24.4 (10.8-39.6)		31.32±6.00	30.7 (20.2-50.8)	

cOne-Way ANOVA test, GH: Genital hiatus, PB: Perineal body, SD: Standard deviation, min-max: Minimum-maximum

measurements in the group suffering from prolapse were detected to be positively correlated with age, whereas PB lengths were found to have a negative association, and GH and PB values were not compared with these variables in the group without prolapse (20).

A study including 535 patients, investigating PB and GB measurements of patients in two groups prior to prolapse surgery, did not establish a difference between sexually active women and those with no sexual activity. However, the duration of sexual activity of cases was not considered in this study. The status of sexual activity was assessed within the last 3 months (21).

We also evaluated the relationship between GH and PB measurements and vaginal symptoms such as recurrent vaginitis and vaginal flatulence. To the best of our knowledge, no other study has been identified on this matter. Although recurrent vaginitis was less common in nulliparous women, we could not detect any difference between the groups in terms of vaginal flatus. In a study conducted, nonspecific vaginitis was not found to be associated with previous pregnancies, history of abortion, mean number of pregnancies, number of abortions, and years of sexual activity (22). In another study, no difference was found between the group with recurrent bacterial vaginosis and the control group in terms of the number of previous deliveries (23). Participants who had vaginal and cesarean deliveries were compared in a study conducted on 942 patients, and similar to our findings, no variance was shown with regard to vaginal flatus (9). Likewise, in another study with 341 cases included, the characteristics of patients with and without vaginal flatus were analyzed. There was no difference in these patients with regard to cesarean and vaginal deliveries (10). More and larger studies are required because vaginal flatus is the newly identified symptom. The small number of patients and the fact that multiparous cases were not included in the study are the most important limitations of our study.

CONCLUSION

Based on the results of our study, the mean GH value was 23.8 mm and the average PH length was 31.1 mm in Turkish women. Further comprehensive studies are needed worldwide to determine whether GH and PB measurements vary between races.

When the results of our study were evaluated, GH enlargement due to single vaginal delivery, mediolateral episiotomy, age and weight, and recurrent vaginitis were less common in nulliparous patients. This finding was accepted as supporting data of that vaginal childbirth has been a factor in leading to POP. Even if we do not find it related, increased GH may disrupt the defense mechanisms of the vagina and increase the risk of infection and vaginal flatus, especially in multiparous cases. We believe that it is important to increase primiparous births without performing episiotomy and to control weight. Our study is the first on this subject. However, more extensive research is required to investigate the relationship between GH and PB measurements and these symptoms.

ETHICS

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2021-03-19, date: 01.02.2021).

Informed Consent: Informed consent was obtained from the patients.

Authorship Contributions

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

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. Uptodate: Surgical female urogenital anatomy. Available from: https://www.uptodate.com/contents/surgical-female-urogenital-anatomy?source=history_widget -14-August-2022
2. Haylen BT, Maher CF, Barber MD, Camargo S, Dandolu V, Digesu A, et al. An International Urogynecological Association (IUGA) / International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP). Int Urogynecol J 2016;27:165-94.
3. Pelvic Organ Prolapse. Hoffman B, Schorge J, Bradshaw K, Halvorson L, Schaffer J, Corton M, editors. In: Williams Gynecology. 3rd ed. McGraw-Hill; 2016. p. 636.
4. Gynecological Infection. Hoffman B, Schorge J, Bradshaw K, Halvorson L, Schaffer J, Corton M, editors. In: Williams Gynecology. 3rd ed. McGraw-Hill; 2016. p. 64-5.
5. Coco AS, Vandenbosche M. Infectious vaginitis. An accurate diagnosis is essential and attainable. Postgrad Med 2000;107:63-6.
6. CDC, Diseases Characterized by Vulvovaginal Itching, Burning, Irritation, Odor or Discharge Available from: https://www.cdc.gov/std/treatment-guidelines/vaginal- discharge.htm Accessed: 14.08.2022.
7. Sultan AH, Monga A, Lee J, Emmanuel A, Norton C, Santoro G, et al. An International Urogynecological Association (IUGA)/

International Continence Society (ICS) joint report on the terminology for female anorectal dysfunction. Int Urogynecol J 2017;28:5-31.

8. Krissi H, Medina C, Stanton SL. Vaginal wind - a new pelvic symptom. Int Urogynecol J Pelvic Floor Dysfunct 2003;14:399-402.
9. Veisi F, Rezavand N, Zangeneh M, Malekkhosravi S, Rezaei M. Vaginal flatus and the associated risk factors in Iranian women: a main research article. ISRN Obstet Gynecol 2012;2012:802648.
10. Lau HH, Su TH, Chen YY, Huang WC. The Prevalence of Vaginal Flatus in Women With Pelvic Floor Disorders and Its Impact on Sexual Function. J Sex Med 2021;18:487-92.
11. Dua A, Whitworth M, Dugdale A, Hill S. Perineal length: norms in gravid women in the first stage of labour. Int Urogynecol J Pelvic Floor Dysfunct 2009;20:1361-4.
12. Trinh AT, Nippita TA, Dien TN, Morris JM, Roberts CL. Perineal length among Vietnamese women. Taiwan J Obstet Gynecol 2017;56:613-7.
13. Lai CY, Cheung HW, Hsi Lao TT, Lau TK, Leung TY. Is the policy of restrictive episiotomy generalisable? A prospective observational study. J Matern Fetal Neonatal Med 2009;22:1116-21.
14. Handa VL, Blomquist JL, Roem J, Muňoz A. Longitudinal study of quantitative changes in pelvic organ support among parous women. Am J Obstet Gynecol 2018;218:320.
15. Fairchild PS, Low LK, Kowalk KM, Kolenic GE, DeLancey JO, Fenner DE. Defining "normal recovery" of pelvic floor function and appearance in a high-risk vaginal delivery cohort. Int Urogynecol J 2020;31:495-504.
16. Young N, Atan IK, Rojas RG, Dietz HP. Obesity: how much does it matter for female pelvic organ prolapse? Int Urogynecol J 2018;29:1129-34.
17. Kim BH, Lee SB, Na ED, Kim HC. Correlation between obesity and pelvic organ prolapse in Korean women. Obstet Gynecol Sci 2020;63:719-25.
18. Aytan H, Tok EC, Ertunc D, Yasa O. The effect of episiotomy on pelvic organ prolapse assessed by pelvic organ prolapse quantification system. Eur J Obstet Gynecol Reprod Biol 2014;173:34-7.
19. Dunivan GC, Lyons KE, Jeppson PC, Ninivaggio CS, Komesu YM, Alba FM, et al. Pelvic Organ Prolapse Stage and the Relationship to Genital Hiatus and Perineal Body Measurements. Female Pelvic Med Reconstr Surg 2016;22:497-500.
20. Kim CM, Jeon MJ, Chung DJ, Kim SK, Kim JW, Bai SW. Risk factors for pelvic organ prolapse. Int J Gynaecol Obstet 2007;98:248-51.
21. Edenfield AL, Levin PJ, Dieter AA, Amundsen CL, Siddiqui NY. Sexual activity and vaginal topography in women with symptomatic pelvic floor disorders. J Sex Med 2015;12:416-23.
22. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med 1983;74:14-22.
23. Hansen JG, Schmidt H. Vaginal discharge and Gardnerella vaginalis. Predisposing factors. Scand J Prim Health Care 1985;3:141-3.

2023 Referee Index - 2023 Hakem İndeksi

Abdullah Hızır Yavuzsan
Ahmet Alptekin
Ahmet Atilla Abdioğlu
Ahmet Cem Esmer
Ahmet Duran Ataş
Ali Karayağmurlu
Ali Aycan Kavala
Ali Fatih Ramazanoğlu
Alkan Bayrak
Alper Bitkin
Arzu Özdemir
Aslı Tok Özen
Asuman Gedikbaşı
Ayşe Süleyman
Ayşe Bahadır
Aysegül Akdoğan Gemici
Başar Burak Çakmur
Bekir Aras
Berrin Berçik İnal
Bülent Güçyetmez
Can Yılmaz Yozgat
Ceren Can
Çiğdem Selçukcan Erol
Çiğdem Toprak
Deniz EsinTekcan Şanlı
Derviş Daşdelen
Derya Atik
Devrim Ulas Urut
Doğan Güçlühan Güçlü
Dolunay Gülmez Kıvanç
Ebru Erzurumluoğlu
Ebru Kale
Ebru Kutsal Kolsal
Eda Kılınç İşleyen
Eda Mengen Uçaktürk
Elif Tanrıverdi
Elif Üner
Emre Baca
Ercan Akşit
Eren Yıldızhan
Ersen Karakılıç
Ertuğrul Okuyan
Esra Deniz Papatya Çakır
Eviç Zeynep Başar
Eyüp Gemici
Fatma Ayşen Eren
Fatma Gül Demirkan
Fatma Ketenci Gencer
Ferit Böyük
Figen Demir
Figen Palabıyık
Figen Çalışkan
Furkan Tontu
Gökhan Sertçakacılar
Gökhan Yılmaz
Gül Karadağ
Gülay Gülbol Duran
Güneş Özlem Yıldız
Habip Gedik
Hafize Emine Sönmez
Hakan Güraslan
Hamide Pişkinpaşa
Hasan Hüseyin Mutlu
Hasret Ayyıldız Civan
Hatice İkiışık
Hatice İncebıyık
Hatice Kutbay Özçelik
Hilal Telli
Hülya Olgun
İbrahim Ece
İbrahim Yıldız
İrem Nur Özdemir
İsa Aykut Özdemir
Jülide Ergil
Keziban Doğan
M. Murat Sayın
Malik Çelik
Mediha Gönenç Ortaköylü
Mehmet Tercan
Mehmet Yürüyen
Mehmet Beşiroğlu
Mehmet Hanifi Kazancı
Mehmet Süleyman Sabaz
Melike Ersoy
Meltem Erol
Meral Mert
Mevlüt Özgür Taşkapılıoğlu
Müge Çatıkkaş
Muhammed Fatih Önsüz
Muhterem Duyu
Murad Asiltürk
Murat Ekin
Murat Muhçu
Murat Uğurlucan
Murat Şakir Ekşi
Musa Çırak
Mustafa Ahmet Afacan
Mustafa Alper Karalök
Mustafa Çakan
Mustafa Çakır
Mustafa Gökhan Bilgili
Mustafa Uygar Kalaycı
Mutlu Uysal Yazıcı
Nafiye Emel Çakar
Nazan Aydın
Neşe Kıskaç
Neslihan Eşkut
Nesrin Gündüz
Nevin Hatipoğlu
Nezih Ziroğlu
Nihat Müjdat Hökenek

2023 Referee Index - 2023 Hakem İndeksi

Nilay İşitez
Nural Kiper
Olcay Ünver
Ömer Faruk Beşer
Osman Murat İpek
Özlem Akgün
Özlem Harmankaya
Özlem Turhan İyidir
Özlem Altuntaş Aydın
Pelin Aytan
Perran Boran
Pınar Yılmazbaş
Pınar Diydem Yılmaz
Pınar Solmaz Hasdemir
Ramazan Korkusuz
Ramazan Sarı
Saygin Türkyılmaz
Seda Turgut
Semra Işık
Semra Yılmaz
Şengül Tural
Serbülent Yiğit
Serpil Çolak
Sevgi Sipahi Çimen
Şevket Ballı
Seyit Ali Büyüktuna
Sezen Avtan
Sibel Serin
Sinan Tüfekci
Şöhret Ferda Kahveci
Süheyla Abitağaoğlu
Şükrü Çekiç
Süleyman Bayraktar
Suna Ors Kokurcan
Tayfun Kara
Tolga Onay
Uzay Erdoğan
Yavuz Demiraran
Yiğit Kültür
Yılmaz Yozgat
Yunus Çolakoğlu
Yusuf Arıkan
Zahide Mail Gürkan
Zeynep Ülker Tamay
Zuhal Yeşilbağ

2023 Author Index - 2023 Yazar İndeksi

2023 Author Index - 2023 Yazar İndeksi

2023 Subject Index - 2023 Konu İndeksi

2023 Subject Index - 2023 Konu İndeksi

2023 Subject Index - 2023 Konu İndeksi

2023 Subject Index - 2023 Konu İndeksi