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Research

Comparison of Mechanical Power Calculations of Volume Control and Pressure Regulated Volume Control Modes: A Prospective Observational Study

Volüm Kontrollü ve Basınç Regüle Volüm Kontrol Modlarının Mekanik Güçlerinin Karşılaştırılması: Prospektif Gözlemsel Çalışma

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ABSTRACT

Objective: Mechanical ventilation is a life-saving practice in acute respiratory distress syndrome (ARDS) patients. However, if not used properly, it causes ventilator-induced lung injury (VILI). Therefore, mechanical power (MP), which combines different variables associated with VILI in a single parameter and is affects mortality, is important in the management of patients with ARDS. In this study, MP values calculated over pressure-volume loops of volume control (VCV) and pressure regulated volume control (PRVC) modes were compared.

Methods: While 36 patients received controlled mechanical ventilation support (VCV and PRVC) under deep sedation, in the supine position on the second day of their intensive care unit hospitalization, MP values were calculated from minute respiratory mechanics. After calculating the 60-minute MP of the patients in the VCV mode with the (MP_{vcv}) (simpl) formula, they were switched to the PRVC mode and the 60-minute MP values were calculated with the MP_{prvc} (simpl) formula. The opposite was done for patients initially ventilated in the PRVC mode. In this way, two dependent groups were formed. All data of 36 patients registered in the 'Metasivionback server' were transferred to Excel with Structured Query Language, and then the patient averages were obtained and compared with the paired t-test.

Results: MP ($p<0.0001$), work of breathing ventilatory ($p<0.0001$) mean values were found to be statistically significantly higher in the PRVC group than in the VCV group. Peak airway pressure ($p<0.0001$) mean values in the VCV group were found to be statistically significantly higher than those in the PRVC group. No significant difference was found between other respiratory parameters.

Conclusion: Although the respiratory parameters (tidal volume, drive pressure and respiratory rate) that contribute to the calculation of MP are similar, lower power values are calculated in VCV mode compared to PRVC.

Keywords: Volume control, pressure control, mechanical power, ventilation, driving pressure

ÖZ

Amaç: Mekanik ventilasyon akut respiratuvar distres sendromu (ARDS) hastalarında hayat kurtarıcı bir uygulamadır. Ancak doğru kullanılmadığında ventilatörün indüklediği akciğer hasarına (VİLİ) neden olmaktadır. Bu nedenle, VİLİ ile ilişkisi saptanan farklı değişkenleri tek bir parametrede birleştiren ve mortalite üzerinde de etkisi olduğu düşünülen mekanik güç (MG) kavramı, ARDS hastalarının yönetiminde önem taşımaktadır. Bu çalışmada, volüm kontrol (VCV) ve basınç regüle volüm kontrol (PRVC) modlarının basınç-volüm döngüleri üzerinden hesaplanan MG değerleri karşılaştırılmıştır.

Gereç ve Yöntem: Yoğun bakım yatışlarının 2. gününde derin sedasyon altında, sırt üstü yatar pozisyonda ve kontrole modlarda (VCV ve PRVC) ventilasyon desteği alan 36 hastanın dakikalık solunum mekaniklerinden MG değerleri hesaplanmıştır. Başlangıçta VCV modundaki hastaların 60 dakikalık mekanik güçleri (basitleştirilmiş) formülü ile hesaplandıktan sonra hastalar PRVC moduna alınmış ve 60 dakikalık mekanik güç değerleri (basitleştirilmiş) formülü ile hesaplanmıştır. Başlangıçta PRVC modunda ventile edilen hastalar için ise tam tersi yapılmıştır. Bu şekilde bağımlı

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2 grup oluşturulmuştur. "Metasivion sunucusu"na kayıtlı 36 hastanın tüm verileri yapılandırılmış sorgu dili sorgulama dili ile elde edilip Excel programına aktarıldıktan sonra hasta ortalamaları alınarak paired t-testi ile karşılaştırılmıştır.

Bulgular: PRVC grubunda MG (p<0,0001) ve ventilatör tarafından hesaplanan solunum işi (p<0,0001) ortalama değerleri VCV grubuna göre istatistiksel olarak anlamlı yüksek bulunmuştur. VCV grubunda tepe hava yolu basıncı (p<0,0001) ortalama değerleri PRVC grubuna göre istatistiksel olarak anlamlı yüksek bulunmuştur. Diğer solunum parametreleri arasında anlamlı fark saptanmamıştır.

Sonuç: Mekanik güç hesaplanmasına katkısı olan solunum parametreleri (tidal volüm, sürücü basınç ve solunum sayısı) benzer olmasına rağmen VCV modunda PRVC'ye göre daha düşük mekanik güç değerleri hesaplanmıştır.

Anahtar Kelimeler: Volüm kontrol, basınç kontrol, mekanik güç, ventilasyon, sürücü basınç

INTRODUCTION

The management of acute respiratory distress syndrome (ARDS), which is one of the important problems in the intensive care unit (ICU), has been the subject of intense discussion in the pandemic (1). Commonly used modes in mechanically ventilated patients in the ICU are volume control ventilation (VCV) and pressure regulated volume control ventilation (PRVC).

Mechanical ventilation is life-saving in patients with ARDS (2). However, if not used properly, it can cause ventilator-induced lung injury (VILI), which has an undesirable outcome (3,4). Therefore, lung protective ventilation practices have been developed to minimize VILI in patients with ARDS (5,6). The protective mechanical ventilation strategy provides the necessary oxygenation that will not cause hypoventilation for the patient without causing trauma to the lung (barotrauma, volutrauma, atalectotrauma) (7). For this reason, the orientation to protective ventilation strategies has increased considering experience and scientific data from the past to the present (8). Today, the concept of 'less is more' has gained importance (5,8). Gattinoni et al. (8) combined different variables, such as tidal volume (TV), driving pressure (DP), gas flow, respiratory rate (RR), and positive end-expiratory pressure (PEEP), which were associated with VILI in various studies, into a single parameter and termed the damage caused by mechanical power MP as ergotrauma (9-13). MP has been associated with increased mortality in intensive care patients (14). It is recommended to keep MP below 12 J/min in patients with ARDS and below 17 J/min in non-ARDS patients (15). For this reason, in the future, MP measurements will be routinely calculated on mechanical ventilator screens and will guide current protective ventilation strategies (8). MP is calculated from the pressure-volume curve (P-V loop) (7). Since the P-V loops of the VCV and PRVC modes are different, it is thought that the formulas developed for the VCV cannot be used for PRVC in the calculation of MP (16). Therefore, different formulae are derived for the VCV and PRVC modes (4,9,17-23).

In this study, the simplified MP equation [$MP_{vcv(simpl)}$] developed by Gattinoni et al. (9) was used for the VCV and the simplified MP equation [$MP_{prvc(simpl)}$] developed by Becher et al. (19) was used for the PRVC mode in MP calculations. Thus, the MP applied to the lung in the VCV and PRVC modes were compared.

METHODS

Ethical committee approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2019-02-23, date: 21.01.2019). Informing and consent forms of all patients that the patient data will be used in prospective scientific studies during the ICU admission were signed by the relatives of the patients. This study was registered at ClinicalTrials.gov (NCT05494554).

Inclusion Criterias

Patients with confirmed coronavirus disease-2019 (COVID-19) diagnosis in ICU admission and diagnosed with ARDS according to the Berlin criteria (24),

Intubated patients were followed up in the supine position on the second day of ICU hospitalization.

Exclusion Criteria

Patients with a known diagnosis of chronic obstructive pulmonary disease,

Patients with unstable hemodynamics during mechanical ventilation,

Patients receiving inotropic support,

Patients with missing data.

Obtaining Patient Data

This study was conducted prospectively with 36 COVID-19 related patients with ARDS who were intubated and diagnosed with ARDS according to the Berlin criteria, in the ICU of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (24). The definite COVID-19 diagnosis was confirmed by PCR (Bio-

Speedy Covid-19 RT-Qpcr detection Kit-Bioeksen, Türkiye) obtained from the nasal swab sample and chest computed tomography images. All patients were ventilated with Maquet Servo-i (Sweden) ventilators. The ventilator parameters of the patients are MP, work of breathing ventilatory (WOBv, automatically measured by the ventilator), inspiratory airway pressure (ΔPinsp), [DP, plateau pressure (Pplato)-PEEP for VCV and fixed ΔPinsp preset for PRVC], PEEP, mean airway pressure [(Pmean, calculated by ventilator: [(peak airway pressure (Ppeak)- PEEP) x (Tinsp/Ttotal)+ PEEP] for PRVC and [(Ppeak- PEEP) x 1/2 x (Tinsp/Ttotal) + PEEP)] for VCV], Ppeak, Pplato, expiratory tidal volume (TVe), PEEP, RR, expiratory minute volume (MVe), end-expiratory gas flow (Vee), inspiration/expiration ratio (I:E ratio), inspiratory rise time (Tslope) were recorded instantly in ImdSoft-Metavision/ QlinICU Clinical Decision Support Software (Canada). Later, these data were obtained from 'Metasivion back server' with Structured Query Language queries and transferred to an Excel file.

While 36 patients received controlled mechanical ventilation support (VCV and PRVC) under deep sedation, in the supine position on the second day of their ICU hospitalization, MP values were calculated from minute respiratory mechanics. If the patient is ventilated in VCV mode, after 60 min of respiratory mechanics and MP values were obtained, it is switched to PRVC mode for 60 min without changing the ventilator settings (RR, PEEP, I:E ratio). Likewise, if the patient is ventilated in PRVC mode, it is switched to VCV mode for 60 min after 60 min of MP calculation in PRVC. Thus, two dependent groups were formed. MP values were calculated from the minute respiratory parameters of all patients with the MP formulas defined in the software. Statistical analyses were performed after taking the patient averages of the 60-minute respiratory parameters (including MP) of both groups.

Calculation of Mechanical Power

This power applied by the ventilator is calculated from the P-V loop area between the airway pressure measured in inspiration and the volume axis (9). Since the P-V loop areas of the VCV and PRVC are not the same, the equations used to calculate the MP are also different (4,9,17-23).

In this study, a simplified volume control power equation [$MP_{vcv(simpl)}$] developed by Gattinoni et al. (9) was used to calculate MP in VCV mode (9). For the PRVC mode, the simplified pressure control power equation [$MP_{prvc(simpl)}$] developed by Becher et al. (19), which assumes that the pressure wave is in the form of an ideal square, was used (16).

Calculation of MP for VCV:

$MP_{vcv\ (simpl)} = 0.098 \times \Delta V \times RR \times (Ppeak - DP/2)$ (9)

Calculation of MP for PRVC:

$MP_{prvc(simpl)} = 0.098 \times RR \times \Delta V \times (\Delta P_{insp} + PEEP)$ (19)

(MP: mechanical power, 0.098= conversion factor, RR: respiratory rate, ΔV: tidal volume, Ppeak: peak airway pressure, Pplato: plato pressure, DP: driving pressure, ΔPinsp: pressure above PEEP during pressure-controlled ventilation)

Statistical Analysis

Descriptive statistical methods [mean, standard deviation (SD), percentage] were used while evaluating the demographic data. The homogeneity of the data was evaluated with the Shapiro-Wilk test. The sample size was calculated as 36 patients based on a pilot study (power =95%; α =0.05) (G*Power version 3.1.9.4, Germany). Respiratory mechanics and MP values of both dependent groups were distributed homogeneously and were compared with the paired t-test. A p-value <0.05 was considered significant. Graphpad Prism 9 (San Diego, USA) was used for statistical analysis.

RESULTS

This study was conducted with 36 patients. The characteristics of the patients included in the study are shown in Table 1.

Mean/SD and p-values of all parameters are shown in Table 2.

Mean values of MP (<0.0001) and WOBv (p<0.0001) were significantly higher in the PRVC group than in the VCV group (Table 2).

Mean values of Ppeak (p<0.0001) were significantly higher in the VCV group than in the PRVC group (Table 2).

Mean values of lung compliance (p=0.466), DP (p=0.772), Pplato (p=0.879), TVe (p=0.927), PEEP (p=0.442), RR (p=0.175), MVe (p=0.373), Vee (p=0.497), I:E ratio (p=0.101), Tslope (p=0.621) did not differ between the VCV and PRVC groups (Table 2).

DISCUSSION

In the previous studies, the superiority of the VCV and PRVC modes to each other could not be demonstrated. There is still disagreement about which mode is better.

In this study, although all respiratory parameters contributing to the calculation of MP (RR, PEEP, Pplato, TVe, DP, I:E ratio) were equal between both ventilation modes (VCV

and PRVC), there was a statistically and clinically significant difference between mechanical power values. The lower MP calculation in the VCV group was attributed to the geometric difference in the P-V loops of both modes (16). In the study by Giosa et al. (17) in which they compared the VCV corrected surrogate MP formula ($MP_{surr.corr}$) with the VCV simplified power formula [$MP_{vcv(simpl)}$] at 5 and 15 cmH_2O values, they found that both formulas calculated power values very close to each other in VCV (17). Chiemello et al. (7), in their study comparing the $MP_{surr.corr}$ formula and the geometric method, compared VCV and PRVC modes at a constant gas flow of 30 L/min. MPs calculated by the geometric method were 7.91±1.98 J/min and 7.84±2.39 J/min in VCV and PRVC modes, respectively. In the same study, MPs calculated with $MP_{surr.corr}$ formula were 7.91±2.06 J/min and 8.64±2.62 J/min in VCV and PRVC modes, respectively (7). These differences were not considered clinically significant. That study suggests that a single formula can be used for both VCV and PRVC to calculate MP (7). In our study, calculated MP values (13.1±2.7 J/min vs 16.3±3.2 J/min for VCV and PRVC, respectively) are almost twice as large as the results of the above-mentioned study, and the power difference between the two modes is equally large. These differences were evaluated as statistically and clinically significant. Therefore, the idea of using the same formula for both modes suggested by Chiumello et al. (7) may not be correct as the difference between the VCV and PRVC modes becomes wider at high power values.

Recently, it has been pointed out that the flow pattern is as important as the flow rate (25). When evaluated in terms of MP, the decelerating gas flow pattern in PRVC causes higher power values compared to VCV even with

Table 1. Demographic data of the patients

Patient characteristics (no=36)	Mean/SD
Female (%)	12 (33.3%)
Age (year)	52±16
Height (cm)	172±8
Predcted body weight (kg/m^2)	63±9
APACHE-II -first	21±7
APACHE-II -last	24±12
APACHE-II -mortality (%)	43±21
SOFA-first	11±4
SOFA-last	11±6
Length of stay in ICU (hours)	342±188
ICU mortality (%)	24 (63.2%)

SD: Standard deviation, APACHE-II: Acute physiology and chronic health evaluation-II, ICU: Intensive care unit, SOFA: Sequential organ failure assessment score

Table 2. Patient averages of respiratory parameters recorded in VCV (60 min) and PRVC (60 min) modes were compared with the paired t-test

Respiratory parameters	VCV (n=36) Mean/SD	PRVC (n=36) Mean/SD	p-value
Mechanical power (J/minute)	13.1±2.7	16.3±3.2	<0.0001
Work of breathing ventilatory (J)	1.15±0.19	1.37±0.21	<0.0001
Lung compliance (mL/cmH_2O)	30.61±9.14	29.83±9.369	0.466
Driving pressure (cmH_2O)	15.95±3.19	16.05±2.46	0.772
Peak airway pressure (cmH_2O)	28.69±3.37	24.80±2.81	<0.0001
Plato pressure (cmH_2O)	24.75±2.93	24.80±2.81	0.879
Expiratory tidal volume (mL)	429.7±55.85	428.6±74.55	0.927
Positive end-expiratory pressure (cmH_2O)	8.801±1.486	8.610±1.460	0.442
Respiratory rate (1/minute)	16.1±1.6	15.7±1.57	0.175
Expiratory minute volume (L/minute)	6.92±1.13	6.71±1.19	0.373
End-expiratory gas flow (L/second)	0.02±0.01	0.02±0.01	0.497
Inspiration/Expiration ratio	0.8±0.16	0.78±0.18	0.101
Inspiratory rise time (Ramp) (Tslope) (second)	0.2±0.11	0.19±0.06	0.621
Gas flow for VCV L/second	0.42±0.11	-	-

VCV: Volume control ventilation, PRVC: Pressure regulated volume control ventilation, SD: Standard deviation

similar respiratory parameters. Because the high flow spikes in the PRVC mode, namely, the high gas flow applied in a short time, has a damaging effect (26,27). Additionally, the rapid transmission of cycle energy to the lungs in early inspiration may have an increasing effect on lung damage (25). This effect is more prominent in patients with ARDS than in patients with homogeneous lungs. It is an ongoing debate whether the decelerating flow pattern may put PRVC at a disadvantage (26).

The geometric method is the gold standard for MP calculation, but the measurement equipment was lacking.

CONCLUSION

Although respiratory parameters (TV, drive pressure and RR) that contribute to the calculation of mechanical power are similar, MP values in the VCV mode are both clinically and statistically lower than PRVC. Although the clinical superiority of the VCV and PRVC modes to each other has not been demonstrated, it is thought that VCV is more advantageous in terms of mechanical power values. Moreover, a single formula for calculating power at high power values will cause inaccurate measurements.

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ETHICS

Ethics Committee Approval: Ethical committee approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2019-02-23, date: 21.01.2019). The research conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Brazil 2013).

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

Authorship Contributions

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

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Research

An Interactive Way to Understand Dementia: Multimodal Experiential Learning Approach in Gerontology Education

Demansı Anlamanın İnteraktif Yolu: Gerontoloji Eğitiminde Çok Boyutlu Deneyimsel Öğrenme Yaklaşımı

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ABSTRACT

Objective: In parallel with the aging population, it will be necessary to provide health care to an increasing number of dementia patients in the coming years. It is critical to develop a gerontology education perspective and change it in accordance with the possibilities of the age. The simulation-based learning method provides an opportunity for experiential learning in education. There is quite a few data on how dementia simulation education improves attitudes toward dementia. We examined how a simulation education program changed students' attitudes toward communication, empathy, and dementia with individuals with dementia.

Methods: This quantitative study investigated undergraduate students' change in awareness of dementia before and after participating in the educational intervention. This study employed a one-group repeated-measures design. A non-virtual, applied dementia simulation program consisting of eight stations was studied with gerontology third and fourth years 116 students. The data were collected by applying the Personal Information form, Dementia Attitude scale (DAS), Empathy Quotient scale (EQS), and The Evaluation Scale of Education Program (ESEP).

Results: DAS and EQS scores were significantly higher after the theorical (p_{DAS}=0.000; p_{EQS}=0.000) and practical education (p_{DAS}=0.000; p_{EQS}=0.000) than before the theorical (p_{DAS}=0.000; p_{EQS}=0.000) and practical education. DAS, EQS, and ESEP scores significantly higher after practical education than after the theorical one (p_{DAS}=0.000; p_{EQS}=0.000; p_{ESEP}=0.000).

Conclusion: Results; points out that dementia simulation helps students understand the experiences of people living with dementia, develop empathetic attitudes, and that dementia simulation education complements and improves traditional teaching methods. Based on these findings, we recommend an applied learning process that includes dementia simulation in addition to classical methods in gerontology education.

Keywords: Dementia, simulation, gerontology education

ÖZ

Amaç: Yaşlanan nüfusa paralel olarak önümüzdeki yıllarda giderek artan sayıda demans hastasına sağlık hizmeti verilmesi gerekecektir. Bu açıdan gerontoloji eğitiminin çağın imkanlarına göre geliştirilmesi ve değiştirilmesi kritik öneme sahiptir. Simülasyon tabanlı öğrenme yöntemi eğitimde deneyimsel öğrenme olanağı sağlar. Demans simülasyon eğitiminin demansa yönelik tutumları nasıl geliştirdiğine dair oldukça az veri bulunmaktadır. Bu çalışmada; bir simülasyon eğitim programının gerontoloji bölümü öğrencilerinin demanslı bireylerle iletişim, empati ve demansa yönelik tutumlarını nasıl değiştirdiğini incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Bu nicel çalışma lisans öğrencilerinin demans farkındalığındaki değişimi ölçmek üzere teorik ve uygulamalı eğitim yapılmadan önce ve sonra çeşitli ölçüm araçlarını kullanılarak yürütülmüştür. Bu çalışma tek gruplu ön test, son test desenindedir. Sekiz istasyondan oluşan gerçek zamanlı, uygulamalı bir demans simülasyon programı 116 gerontoloji üçüncü ve dördüncü sınıf öğrencisi ile çalışılmıştır. Veriler Sosyodemografik Veri formu, Demans Tutum ölçeği (DTÖ), Empati Düzeyi Belirleme ölçeği (EDBÖ) ve Eğitim Programlarını Değerlendirme ölçeği (EPDÖ) uygulanarak toplanmıştır.

Bulgular: DTÖ ve EDBÖ skorları; teorik eğitim sonra ($p_{DTÖ}$=0,000; $p_{EDBÖ}$=0,000) ve pratik eğitimden sonra ($p_{DTÖ}$=0,000; $p_{EDBÖ}$=0,000) teorik ve pratik eğitim öncesine göre anlamlı derecede daha yüksek bulundu. Ayrıca DTÖ, EDBÖ ve EPDÖ puanları da pratik eğitimden sonra teorik eğitim sonrasına göre anlamlı derecede daha yüksek bulundu ($p_{DTÖ}$=0,000; $p_{EDBÖ}$=0,000; $p_{EPDÖ}$=0,000).

Sonuç: Sonuçlar demans simülasyonunun, öğrencilerin demans hastalarının deneyimlerini anlamalarına, empatik tutumlar geliştirmelerine yardımcı olduğuna ve demans simülasyon eğitiminin geleneksel öğretim yöntemlerini tamamlayıp geliştirdiğine işaret etmektedir.

Anahtar Kelimeler: Demans, simülasyon, gerontoloji eğitimi

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INTRODUCTION

The Need and Innovation for Education of Dementia Care in Gerontology Education

Institutions and organizations that provide health services do not have enough educational equipment to meet the needs of patients with dementia patients (1). Similarly, it can not be said that gerontology education curricula train well-equipped gerontologists about dementia.

In the 21st century, the biggest challenge expected in aging populations is predicted to be the clinical problems arising from neurodegenerative changes, which inherently increase with advanced age (2). The increased percentage of the elderly in the general population is an important indicator of the future increase in the demand for dementia-related services. The incurability of dementia means that people with dementia will increasingly need health services (3).

Dementia describes a cognitive impairment syndrome that affects memory, cognitive abilities, and behavior and significantly interferes with a person's ability to perform daily activities. The majority of dementia cases (63%) live in low- and middle-income countries (4). Dementia is the seventh leading cause of death in the world today. The increase in the number of dementia patients will inevitably bring a burden of care in the coming years. Therefore, researchers should take steps to encourage positive attitudes toward patients with dementia by changing negative attitudes and stereotypes about dementia (5).

Behavioral and Psychological Symptoms of Dementia (BPSD) involve changes in perception, emotion and functioning that contribute to disturbing, abnormal and potentially dangerous behaviors (e.g., wandering, verbal aggression) (6). Their execution is laborious and necessitates a specific skill set, but these non-pharmacological interventions are also essential as first-line treatment for BPSD (7). Health students report having negative feelings toward people with dementia, in particular those exhibiting BPSD, and a lack of confident in managing challenging BPSD behaviors (8,9). BPSD may be aggravated during even healthcare encounters. Instead, better perceiving the intended meaning of patient behaviors resulted in fewer negative responses to BPSD and more problem-solving behaviors (10). In this context, caregiver's attitudes and communication skills toward dementia patients are important. There is a need to realize and admit the person's reality and nurturing authentic relationships (11). Persons with dementia want service providers to recognize them as individuals and to listen to their concerns patiently (12).

Patients with dementia have multiple healthcare needs that require essential practice modifications, such as potential impairment of decision-making capacity, limited communication skills, and the presence of behavioral symptoms. Professionals working with dementia need to know how to meet the healthcare requirements of people with dementia. In this study, we examine how a real -time simulation-based education program called the Hans on Dementia, may prepare gerontologists and how this practice develops gerontology education.

Gerontology Education

The increasing number of older adults is a clear indication of the growing need for healthcare professionals to work in the geriatric and gerontological fields. Studies show that even just taking gerontology courses causes students to report higher proficiency in aging, and they change their attitudes toward accepting working with the aging population in the future (13).

A combination of various learning activities such as case analysis, video-based learning, and clinical praxis with people with dementia was applied in gerontology education (8,14,15). Simulation programs have been part of the gerontological curriculum to help students and healthy individuals understand the limitations faced by the elderly, including sensory modifications to simulate hearing and vision reduction (16,17). However, these applications still do not have a permanent place in the gerontology curriculum. Programs are often used to promote empathy and understanding among students. Some of them are computer-based.

In the transformative learning theory, learning tasks are initiated by a disruptive or transformative event in which learners become aware that their worldview has been distorted (18,19). Then, changes in behavior and attitudes occur following critical self-reflection on why the distortions in the mind of one exists, an emotional process that often involves feelings of guilt. Critical self-reflection leads students to set new criteria for constructing their worldview more accurately. Finally, behavioral changes emerge when students discover new roles for themselves with their updated understanding of the phenomenon. Transformative learning processes are needed for gerontology students to internalize what they have learned. Therefore, it is thought that placing dementia simulation education in gerontology curricula will affect these transformative learning processes.

METHODS

Research Design

This quantitative study measured undergraduate students' self-reported changes in awareness of dementia before

and after participating in the educational intervention using the various measuring instruments. This study used a one-group repeated-measures design. An educational intervention was given by a multidisciplinary team and focused on raising awareness of dementia with follow-up data collection. First, a theorical education is given and then a practical education is given. Outcomes - attitude toward dementia and level of empathy - were measured at baseline, after theorical education and after the practical education.

Participants and Setting

The research was carried out in the spring semester of the 2021-2022 academic year, with 3rd and 4th grade students studying at the Gerontology Department of İstanbul University-Cerrahpaşa for 2 weeks. A total of 116 students who accepted to participate in the study and completed both theorical and practical education constituted the study group. All participants gave written informed consent before data collection.

Instruments

The data of the study were collected by applying the Personal Information Form, Dementia Attitude scale (DAS), Empathy Quotient Scale (EQS), and The Evaluation Scale of Education Program (ESEP) developed by the researcher to the individuals who agreed to participate in the study using a face-to-face data collection technique. The scale implementation took an average of 10-15 min for each participant.

DAS: The DAS was used to evaluate students' attitudes toward dementia. This scale was developed by O'Connor and McFadden (20) in 2010. Response options were scored on a 7-point Likert scale ranging from 1 (strongly disagree) - 7 (strongly agree). The scale consists of 20 items, and 6 items are reversed (2,6,8,9,16,17). The Cronbach's alpha value of the scale was reported to be 0.83 (20). A Turkish validity and reliability study was conducted by Çetinkaya et al. (5). The Cronbach's alpha value of the DAS was 0.84, and it was found that the scale had a high degree of internal consistency. With confirmatory factor analysis, it was confirmed that the scale consisted of three factors: "Supporting Attitude", "Acceptable Attitude" and "Exclusionary Attitude". The total scores for this scale ranged from 20 to 140. As the score increases, the supportive and accepting attitudes increase, whereas the exclusionary attitudes decrease.

EQS: The EQS will be used to determine the empathy levels of the students. This scale was developed by Lawrence et al. in 2004 (21). The scale, which was adapted into Turkish by Kaya and Çolakoğlu (22) in 2015, consists of 13 items and 3 sub-dimensions, 1 of which is reverse coding (3rd item). The factors of the scale were named as Cognitive Empathy (4th, 9th, 11th, 12th, 13th item), Emotional Reactivity (6th, 7th, 8th, 10th item), and Social Skills (1st, 2nd, 3rd, 5 item). The scale is in a four-point Likert type, including "strongly disagree (1), slightly disagree (2), slightly agree (3), and strongly agree (4)". The higher the score obtained from the scale, the higher the level of empathy. Cronbach's alpha for EQS was calculated as 0.78. In this study, the EQS Cronbach's alpha value was calculated as 0.81.

ESEP: The ESEP is a 5-point Likert-type scale (1= I strongly disagree, 5= I totally agree) consisting of 28 items (23). There are two factors on this scale. Factor 1 includes items to evaluate the process, duration, instructor, and interaction related to the education program and is named as "Teaching Process and Acquisitions". There are 21 items in this factor. Factor 2, on the other hand, contains items for evaluating the implementation process of the implemented education program and is called "Organization Design". There are 7 items in this factor. In the scale development study, internal consistency coefficients (Cronbach alpha) were calculated as 0.95 for the entire scale, 0.97 for factor 1 and 0.71 for factor 2. An increase in the score obtained from the scale indicates that the participants' views about the education programs are more positive.

Implementation of the Study

The education to be given to the participants within the extent of the study consists of two stages: theorical and practical. The flow chart of the implementation of the study is shown in Figure 1.

Educational Intervention

Theorical Education: Gerontological Neuropsychiatric Evaluation Education Content

Theorical education was applied to all participants for two days. The education was planned to consist of two sessions before noon and two sessions in the afternoon for both days. Thus, a total of 8 sessions were completed in two days.

The theorical education consists of 4 main modules.

A. Neurological basis of behavior

- Neuroanatomical and neurofunctional aspects of behavior (functional anatomy and networks),
- Brain, cognitive functions and memory.

B. Dementia: diagnosis, differential diagnosis and follow-up

- Dementia,
- Depression,
- Delirium.

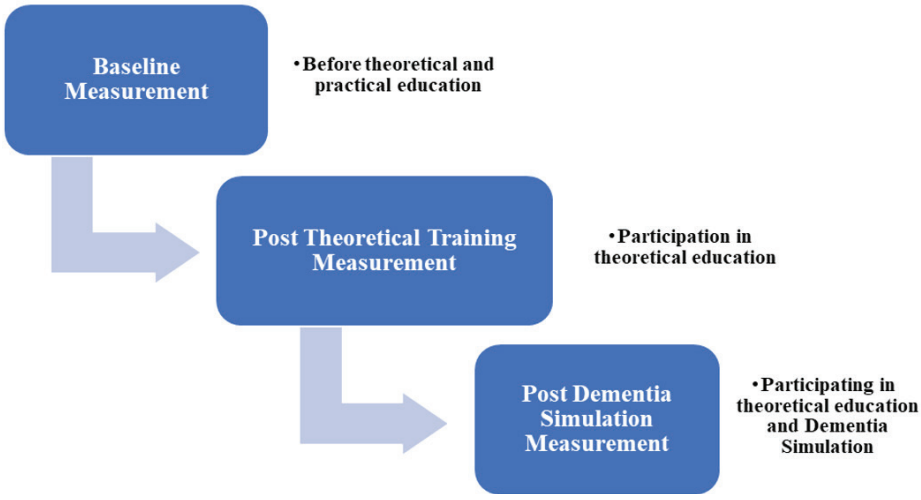

Figure 1. Flow chart

C. Scales used in the field

- Mini Mental State test,
- Instrumental Activities of the Daily Living Scale
- Geriatric Depression Scale (Yesavage).

D. Living with a patient with dementia: communication techniques with a patient with dementia

- Principles and attitudes in interviewing and relationship building,
- Interview tools and principles,
- Communication process in interview,
- Effective communication concepts and process,
- Therapeutic communication skills,
- Empathy skills and empathic communication.

Practical Education: Dementia Simulation Toolkit

Dementia Simulation Toolkit that we used is a face-to-face, real-time practice. Although its effectiveness according to artificial intelligence applications is the subject of another study, one-to-one human contact in education is still irreplaceable. Participants are then given a set of simple tasks to complete over a timed period in a designated simulation space. This is followed by a obtaining information period during which participants are informed about their behavior and reflecting on their experiences during the simulation. According to this theory, the BPSD are the result of a reduced capacity to deal with stress caused by sensory and environmental stimuli. Therefore, participation enables students to foresee stress sources that may contribute to BPSD (24).

This toolkit contains; information facilitators must know regarding dementia and dementia, simulation techniques and sample scenarios based on common experiences of the older adults in the healthcare system, ideas on how to structure the simulation session for an interprofessional audience, including the debrief. This simulation intends to increase a person's awareness of knowledge about cognition and dementia. This simulation can challenge common assumptions and support enhanced empathy and attitudes toward dementia and the elderly. Through reflection during debriefing, participants have the opportunity to consider the implications for practice (24).

Practical education consists of 8 main modules. These 8 modules refer to a group of symptoms that commonly manifest in people with dementia consisting of: anosognosia, agnosia, aphasia, apraxia, altered perception, amnesia, apathy, and attentional deficits. At the simulation stations, the participant works through scenarios (24).

Statistical Analysis

Statistical analysis was performed using SPSS statistical software, version 25.0. Mean, standard deviations (SDs), and/or 95% confidence intervals were calculated for all variables. The Kolmogorov-Smirnov test showed a normal distribution of the data ($p>.05$). Repeated measures analysis of variance was used for variables collected longitudinally at three points (baseline, after theorical education programme and after simulation education programme) to test for change over time in outcome variables. Mauchly's test of Sphericity was non-significant ($p>.05$) and thus the assumption of compound symmetry was met, indicating that the correlations across the measurements were the same and the variances were equal across measurements. Post-hoc analyses using paired t-tests were performed to determine the changes between the baseline and post education program values. Statistical significance was set at $p<0.05$ and all p-values were reported two-sided.

Ethical Approval

Ethics committee approval was received for this study from the Social and Human Sciences Ethics Committee of İstanbul University-Cerrahpaşa (decision no: 2022/350, date: 08.11.2022). The study was conducted in compliance with the principles of the Declaration Helsinki.

RESULTS

A hundred and sixteen participants' data form, who attended the entire training process, were analyzed in this study. Table 1 shows participants' demographic information.

Ninety one participants were females (78.4%) and 25 (21.6%) of them were males. The mean age was 22.44 years (range 20-34; SD: 3.15). Sixty one participants (52.6%) were third class and 55 participants (47.4%) fourth class students.

Table 2 shows participants longitudinally at three points (baseline, after theorical education programme and after simulation education programme) for change over time in outcome variables.

There is a significant difference between the DAS scores of the students who attended the education before the theoretical and practical education, after theorical education (p_{ate}=.000) and after the practical education (p_{ape}=.000). Here, considering the average score;

- DAS scores were found to be significantly lower before theorical and practical education (109.36±12.07) than after theorical education (113.85±13.12) and after the practical education (117.65±12.94). As the score obtained from the scale increases, it is expected that individuals will

Table 1. Participants' demographic information

Variables	Subscales	n	%
Gender	Female	91	78.4%
	Male	25	21.6%
Class	3rd grade	61	52.6%
	4th grade	55	47.4%
Age	22.44±3.15 (minimum-maximum: 20-34)		

Table 2. Outcome variables at three time points (n=116)

	Before theorical and practical education		After the theorical education		After the practical education		F/t	Post-hoc
	x̄±SD	(95% CI)	x̄±SD	(95% CI)	x̄±SD	(95% CI)		
Dementia Attitudes scale	109.36±12.07	(107.14, 111.58)	113.85±13.12	(111.44, 116.27)	117.65±12.94	(115.28, 120.04)	44.070	1-2* 1-3* 2-3*
- Supporting attitude	50.50±5.10	(49.56, 51.43)	51.96±5.34	(50.98, 52.95)	53.15±5.15	(52.21, 54.10)	22.243	1-2* 1-3* 2-3*
- Acceptable attitude	29.90±6.05	(28.79, 31.02)	32.63±6.06	(31.51, 33.74)	34.07±6.51	(32.85, 35.28)	41.952	1-2* 1-3* 2-3*
- Exclusionary attitude	28.96±4.31	(28.16, 29.75)	29.26±4.99	(28.34, 30.18)	30.43±4.88	(29.53, 31.33)	7.170	1-3* 2-3*
Empathy Quotient scale	54.44±6.58	(53.23, 55.65)	55.99±6.86	(54.73, 57.25)	57.40±6.57	(56.19, 58.61)	27.620	1-2* 1-3* 2-3*
- Cognitive empathy	20.27±2.95	(19.72, 20.81)	20.92±3.12	(20.35, 21.50)	21.59±3.17	(21.01, 22.18)	16.658	1-2* 2-3*
- Emotional reactivity	17.36±2.28	(16.94, 17.78)	17.59±2.49	(17.13, 18.05)	18.07±2.13	(17.68, 18.46)	9.994	1-2* 2-3*
- Social skills	16.81±2.53	(16.34, 17.28)	17.48±2.43	(17.04, 17.93)	17.73±2.23	(17.32, 18.14)	14.081	1-2*
The Evaluation Scale of Education Program	-	-	126.86±12.53	(124.36, 128.98)	133.99±8.09	(132.25, 135.41)	-7.270	2-3*
- Teaching process and acquisitions	-	-	97.19±9.27	(95.37, 98.72)	102.68±5.18	(101.65, 103.52)	-7.490	2-3*
- Organization design	-	-	29.67±6.09	(28.52, 30.75)	31.31±5.43	(30.24, 32.29)	-3.001	2-3*

*p<.05. CI: Confidence interval, SD: Standard deviation

better recognize dementia and develop more effective coping skills by displaying more positive attitudes toward individuals with dementia.

- DAS scores were found to be significantly lower after theorical education (113.85±13.12) than after practical education (117.5±12.94). As the score obtained from the scale increases, it is expected that individuals will better recognize dementia and develop more effective coping skills by displaying more positive attitudes toward individuals with dementia.

There is a significant difference between the EQS scores of the students who attended the education before theorical and practical education, after theorical education (p_{ate}=0.000) and after the practical education (p_{ape}=.000). Here, considering the average score;

- EQS scores were found to be significantly lower before theorical and practical education (54.44±6.58) than after theorical education (55.99±6.86) and after the practical education (57.40±6.57). As the score obtained from the scale increases, it is expected that the empathy levels of the participants toward individuals with dementia will be higher.

- EQS scores were found to be significantly lower after theorical education (55.99±6.86) than after practical education (57.40±6.57). As the score obtained from the scale increases, it is expected that the empathy levels of the participants toward individuals with dementia will be higher.

There is a significant difference between the ESEP scores of the students who attended the education after theorical education and after the practical education (p=.000). Here, considering the average score;

- The ESEP scores were found to be significantly lower after theorical education (126.86±12.53) than after practical education (133.99±8.09). As the score obtained from the scale increases, it is expected that the empathy levels of the participants toward individuals with dementia will be higher. As the score obtained from the scale increases, it is expected that the participants' opinions about the education they attend will be more positive.

DISCUSSION

In our study, the results of the DAS of the students show that the students' taking practical education on dementia compared to their only theorical education, and only theorical education rather than no education changed their attitudes toward dementia positively. In the literature, there are studies on different and unique applications in which DAS is used. Studies have shown that 'creative storytelling' sessions of medical students (25) or 'dementia friends' sessions positively change attitudes toward dementia in university students and community members (26). Opening Mind through Arts is another unique practice that shows that the perspective toward dementia have changed positively with the DAS in undergraduate students aged between 18 and 45 in various academic disciplines (27).

In our study, a face-to-face application, originally called Hands on Dementia, simulating eight daily life activities in real time and each carried out at different stations was conducted. The participants experience executive functions such as reasoning and planning, and neurocognitive functions lost in dementia such as attention, apraxia, memory, aphasia, acalculia, and agnosia, through the themes of dressing, breakfast, lunch, in the city, housework, leisure, dinner, and at the end of the day. Stations; were created to enable the participant to experience the typical symptoms of dementia, so that they can understand the troubles and difficulties faced by a person with dementia in their daily life, and how they might have felt, and thus their 'inner world'. The results of our study indicate that the simulation application, which makes gerontology students experience the symptoms of dementia in the most similar way possible, changes the attitudes of the students toward dementia patients positively.

The results of the EQS point out that the fact that they have received practical education for dementia positively changes their empathy levels for dementia patients compared with those who have received only theorical education, and those who have received theorical education compared with those who have not received any education. These results indicate that the educational content for dementia should be included in the gerontology curricula, at least at the theorical level.

In some gerontology departments, students are educated about the difficulties they will encounter while working with dementia patients, and about the points to be considered in communication, or the strategies to care for these patients. But none of this is given from the patient's perspective. Therefore, such a simulation application added to theorical education can close this gap in classical education by increasing empathy toward patients with dementia. Consistent with the quantitative data in our study, students stated that they felt more empathy toward person dementia after participating in the simulation. They were baffled at how difficult it was to complete the simulation tasks and noticed that persons with dementia face these challenges every day.

Empathy corresponds to the critical identification process in the transformative learning process. We think that the effect created by the application stations in the students increases the effectiveness of education. The simulation itself is experienced by students as a transformative-destructive event. In this process, students are affected physically and emotionally as well as cognitively. Therefore, there are demolition and reconstruction.

According to Van Schalkwyk et al. (28), the critical skills required in transformative learning programs conducted with students receiving health education are empathy, trust, and cultural sensitivity. These features are essential for managing person-centered care in clinical settings (28). The achievements of programs are ascribed to the fact that they encourage students to adopt perspectives different from their own to discourage stereotypes. An intern may have a skewed understanding of why someone living with dementia is behaving a certain way (for example, he is already a bad person and dementia has revealed his "true" self). Simulation education can break this assumption. It initiates a self-critical re-evaluation process by removing the students from stereotypes about dementia.

The results of the ESEP show that gerontology students' practical education increases their satisfaction with their education compared with those who only receive theorical education. Adding experiential learning to didactic courses increased students reported educational satisfaction in working with and understanding the challenges of treating patients with dementia. In a similar study conducted with physical therapy students, they found that students' multimodal experiential learning process increased their confidence in understanding the difficulties of working with patients with dementia patients (14).

The use of simulation in gerontology education has emerged as a need discussed for more than twenty years (16). However, in a study with health students on person-centered dementia care with a virtual simulation tour, none of the participants mentioned that the faculty should abandon traditional teaching methods (9). Therefore, such practices integrate the knowledge learned through classical education. We suggest that the curricula of gerontology and similar professionals who will work with patients with dementia should be rearranged to include both practical and theorical education considering our study and data from similar studies.

Note that this study had a limited sample size (116 students) and selection bias (the sample size comes from two class cohorts that are not necessarily representative of the general population of gerontology students). The reason for choosing the third and fourth-year gerontology students is that it would be more appropriate to study the approach to the elderly with dementia with the students who gained the notion of working with the healthy elderly in the first two years of their education. Future research in this area should focus on collecting data from larger samples and should also focus on quantifying the amount of dementia education that is already being carried out in Türkiye and around the world.

CONCLUSION

This study is an example of a successful multimodal experiential learning module for dementia education as well as for education in the health professions. Additionally, students participated in experiential simulation in addition to traditional methods in education. The study findings are critical for gerontology education programs that train gerontologists to work with dementia. Innovative, meaningful, and effective dementia education can improve the treatment of patients with cognitive decline and lead to improved patient outcomes. Although gerontology education programs are different around the worldwide, it is clear that the educational content on dementia should increase in gerontology curricula. Gerontology education curricula should prepare gerontology students for the elderly profiles they will encounter in professional life. With the dementia burden that the increasing older adult population will bring with it, society can cope better with gerontologists trained on this subject.

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ETHICS

Ethics Committee Approval: Ethics committee approval was received for this study from the ESocial and Human Sciences Ethics Committee of İstanbul University-Cerrahpaşa (decision no: 2022/350, date: 08.11.2022). The study was conducted in compliance with the principles of the Declaration Helsinki.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Authorship Contributions

Surgical and Medical Practices: S.Ç., Concept: S.Ç., H.S.I., Design: S.Ç., T.G., Data Collection or Processing: H.S.I., T.G., Analysis or Interpretation: S.Ç., H.S.I., Literature Search: S.Ç., H.S.I., T.G., Writing: S.Ç., H.S.I., T.G.

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Research

Fibrosis Regression Post Direct-acting Antiviral Treatment in Hepatitis C Virus Patients

Hepatit C Virüslü Hastalarında Direkt Etkili Antiviral Tedavi Sonrası Fibrozisin Gerilemesi

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ABSTRACT

Objective: We studied long-term serial changes in aspartate aminotransferase/platelet ratio index (APRI) and fibrosis-4 (FIB-4) scores in hepatitis C virus patients with a sustained virologic response after direct-acting antiviral (DAA) therapy.

Methods: Seventy-five patients treated with DAA were included in this study. APRI and FIB-4 scores were calculated at the beginning of DAA treatment, at the end of treatment (EOT), one and two years after treatment.

Results: Twenty-eight patients had cirrhosis. APRI and FIB-4 scores (1.38 vs. 0.49, p<0.001; 4.25 vs. 2.79, p<0.001) Improved in all patients at the EOT. There was also a trend toward decreased scores for APRI and FIB-4 at follow-up based on EOT of 2nd-year results (APRI, 0.49 vs. 0.41, p=0.87; FIB-4, 2.79 vs. 2.50, p=0.44). There were significant improvements in cirrhotic patients' two-year APRI and FIB-4 scores (0.86 vs. 0.58, p<0.001; 4.74 vs. 3.59, p<0.001). Similarly, in the 1st and second years, APRI and FIB-4 scores were compared after EOT in cirrhotic patients (0.84 vs. 0.58, p=0.007; 4.74 vs. 3.59, p=0.004) and showed remarkable improvement.

Conclusion: Improvements in liver fibrosis markers were prominent in patients with advanced fibrosis. The regression in liver fibrosis based on non-invasive tests has persisted even two years after the treatment.

Keywords: Fibrosis regression, HCV, APRI, FIB-4

ÖZ

Amaç: Çalışmamızda doğrudan etkili antiviral (DAA) sonrası sürekli virolojik yanıt elde eden hepatit C virüsü hastalarında aspartat aminotransferaz/trombosit oran indeksi (APRI) ve fibrozis-4 (FIB-4) skorlarındaki uzun süreli seri değişiklikleri araştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışmaya DAA tedavisi uygulanan 75 hasta dahil edildi. APRI ve FIB-4 skorları, DAA tedavisinin başında, tedavi sonunda (EOT), tedaviden bir ve iki yıl sonra hesaplandı.

Bulgular: Yirmi sekiz hastada siroz vardı. APRI ve FIB-4 skorları [1,38 vs. 0,49, p<0,001; 4,25 vs. 2,79, p<0,001] EOT'deki tüm hastalarda düzeldi. İkinci yıl sonuçlarına göre EOT'ye dayalı takipte APRI ve FIB-4 puanlarında azalma yönünde bir eğilim de vardı (APRI, 0,49 vs. 0,41, p=0,87; FIB-4, 2,79 vs. 2,50, p=0,44). Sirotik hastaların iki yıllık APRI ve FIB-4 skorlarında anlamlı iyileşmeler vardı [0,86 vs. 0,58, p<0,001; 4,74-3,59, p<0,001]. Benzer şekilde 1. ve 2. yıllarda sirotik hastalarda EOT sonrası APRI ve FIB-4 skorları karşılaştırıldığında [0,84 vs.0,58, p=0,007; 4,74 vs. 3,59, p=0,004] hastalarda anlamlı düzelme görüldü.

Sonuç: İlerlemiş fibrozisi olan hastalarda karaciğer fibrozis belirteçlerindeki belirgin iyileşmeler görüldü. İnvaziv olmayan testlere dayanan karaciğer fibrozundaki gerileme, tedaviden iki yıl sonra bile devam etmiştir.

Anahtar Kelimeler: Fibrozis gerilemesi, HCV, APRI, FIB-4

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INTRODUCTION

Hepatitis C virus (HCV) is one of the leading causes of liver-related morbidity and mortality worldwide (1,2). Continued fibrogenesis in the liver often leads to cirrhosis. The risk of hepatocellular carcinomas (HCC) increases with progressive fibrosis, with most cases occurring in patients with advanced fibrosis and/or or cirrhosis (3). Recently, excellent responses have been obtained with the new direct antiviral agents (DAA) used in treating chronic hepatitis C. Thanks to these drugs that directly target the HCV, over 90% sustained virological response (SVR) has been achieved (4). Because of DAA-based treatments, it has been shown that HCV eradication is achieved, the course of the disease improves, cirrhosis and related complications, and the development of HCC is reduced (5). This result is probably attributed to fibrosis regression after viral eradication (6). The best method for evaluating fibrosis regression is to examine it with liver biopsy. However, it is impractical to perform a liver biopsy to assess the fibrosis stage in all patients. Many non-invasive methods are widely used, including imaging technologies and serum biomarkers. Several laboratory indices, including the aspartate aminotransferase/platelet ratio index (APRI) and fibrosis-4 (FIB-4), are good indicators for using liver fibrosis in patients with chronic HCV infection. The sensitivity and specificity of the FIB-4 and APRI scores have been validated, particularly for chronic hepatitis C (CHC) patients with advanced fibrosis and cirrhosis (7).

It has numerous advantages, such as ease of procedure, reproducibility, patient acceptance, cost-effectiveness, and absence of biopsy-related risks. The aim of this study was to evaluate the dynamics of APRI and FIB-4 (NIT's).

Scores of HCV patients who achieved SVR after receiving DAA and follow-up the course of NIT's screened fibrosis regression in patients with cirrhosis who achieved SVR in the years after treatment.

METHODS

Study Design

The study was planned as a single-centre, retrospective study. Data were analyzed according to changes in FIB-4 and APRI fibrosis scores in patients with CHC treated with DAA therapy.

Ethics Statement

The study was approved by the Ethics and Clinical Research Committee of the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital (decision no: 27-2022, date: 16.02.2022) and conducted following the Declaration of Helsinki.

Study Population

Patients who had DAA therapy for CHC between December 2016 and December 2019 by University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital Gastroenterology Polyclinic and who achieved a persistent viral response SVR were retrospectively analyzed. We explained SVR as the serum HCV ribonucleic acid (RNA) level that was undetected after discontinuation of treatment in our study. We analyzed laboratory data at the start of DAA treatment, at the end of treatment (EOT), one and two years after treatment. Excluded are the chronic liver disease of a non-HCV aetiology (e.g., autoimmune hepatitis, Wilson's disease, hemochromatosis, diabetes mellitus), viral hepatitis B infection or immunodeficiency virus infections (e.g., human immunodeficiency virus), malignancy and organ transplantation. Additionally, patients with incomplete clinical laboratory data required for non-invasive measurements of liver fibrosis were excluded. Demographic information for each patient, laboratory data, HCV treatment regimen, and SVR history were obtained from medical records.

Non-invasive Measurements of Liver Fibrosis

Two non-invasive biomarkers for fibrosis, APRI, and FIB-4, were calculated before and after SVR based on the following formulas (8).

APRI was calculated with the following formula: [Aspartat aminotransferase (AST) (IU/L)/AST (high limit of normal range-IU/L)/platelet count (10^9/L)] x100, and the patients were sub-grouped due to determined cut-offs from previous studies (<1, 1-2, >2). The used APRI cut-off score was 2 in the detection of cirrhosis (9).

The formula for the calculation of the FIB-4 index was as follows: age (years) x AST (IU/L)/[platelet count (10^9/L)/√ alanine aminotransferase (ALT) (IU/L)]. The previously identified cut-off levels were used to classify patients (<1.45, 1.45-3.25, >3.25). Advanced fibrosis was defined as FIB-4>3.25 (10).

Antiviral Therapy

The patient's presence and degree of cirrhosis, whether the previous treatment is experienced, and the virus genotype, play a role in selecting direct-acting antiviral therapy. The period of treatment was given a duration ranging from 8 to 24 weeks. DAA protocols comprised sofosbuvir (SOF, 400 mg once daily) with ribavirin (RBV, 500 mg /600 mg twice a day); SOF/ledipasvir (LDV) (400 mg/90 mg once daily) ± RBV; The PrOD regimen (paritaprevir 75 mg once daily, ombitasvir 12.5 mg, and ritonavir 50 mg plus dasabuvir

250 mg twice daily) ± RBV; glecaprevir (GLE, 300 mg once daily) plus pibrentasvir (PIB, 120 mg once daily). Treatment duration was 8, 12, or 24 weeks, determined due to baseline genetic and fibrosis grade. The treatment last point was identified as the failure to detect HCV RNA in serum by a sensitive test (less than ≤15 (IU/mL) after the EOT.

Statistical Analysis

Data of the study were analyzed with the inclusion body myositis statistical package for the social sciences statistical 22.0 program. Descriptive analyses are given as percentages and numbers. Because the percentage and frequencies of the study data did not fit the normal distribution in the dependent group analysis, the Wilcoxon test was used in the comparison. A p-value of less than 0.05 was accepted as significant in statistical analysis. If the p-value was very low in the computation, the value is expressed as p<0.001.

RESULTS

Demographic and Clinical Findings

This study included seventy-six patients who had received treatment. Patient demographics and baseline characteristics are shown in Table 1. Of the patients, 32 (42.1%) were male, and 44 (57.9%) were female. The mean age of the patients was 61±13 years. Twenty-eight patients (36.8%) had cirrhosis. Twenty patients (25.9%) were previously treated for HCV infection (treatment-experienced). SVR could not be obtained in one patient who did not complete the treatment. Other than this, 75 patients were determined to have SVR (98.7%). Sixty-three (82.9%) patients were genotype 1 (75% genotype 1b, 7.9% genotype 1a). Additionally, 9 (11.8%) patients were genotype 2, 4 (3.9%) genotype 3, 1 (1.3%) genotype 5. In the TURHEP study published in 2015, in our country most of the CHC patients were genotype 1b (92.1%) (2). 40.8% PrOD, 18.4% LDV/SOF, 11.7% PrOD+RBV, 10.5% SOF+RBV, 9.2% LDV/SOF+RBV and 9.2% used GLE+PIB. The baseline median AST and ALT levels were 55 (36-89) U/L and 52 (40-103) U/L, respectively. The median platelet count was 172 (119-259)×10^9/L. The median HCV RNA level was 9.82 (9.72-14.67) log10 IU/mL, the median APRI value was 1.19 (0.62-2.45), and the median FIB-4 value was 2.93 (1.57-5.80). After EOT, 98% of patients had a SVR (Table 1). The data of 75 patients with SVR, 72 patients with follow-up at one year, and 63 patients with follow-up at two years were evaluated. During the first year, one cirrhotic patient died from cardiac failure, and one non-cirrhotic patient died from a lung abscess. In the second year, two cirrhotic patients died, one due to newly detected HCC secondary hepatic decompensation and the other due to endometrial cancer.

Platelet Count, ALT, and AST Levels at the End of Treatment in Patients with SVR

In patients who received DAA therapy with SVR (n=75), the median platelet count increased at the EOT (p<0.001). The median AST (p=0.002) and ALT (p=0.036) values decreased (Table 2).

Table 1. Patient's demographics and baseline characteristics

Patient's demographics and baseline characteristics	Total cohort (n=76)
	n (%) or median IQR
Sex	
Male	32 (42.1)
Female	44 (57.9)
Age (years) [mean, SD]	61±13
AST (U/L)	55 (33-92)
ALT (U/L)	52 (31-82)
Platelet count (×10^9/L)	172 (119-259)
APRI	0.79 (0.38-1.68)
FIB-4	2.95 (1.54-5.81)
HCV viral load (IU/mL)	9,829,414 (972,19-14,678,475)
HCV genotype	**n (%)**
1A	6 (7.9)
1B	57 (75)
2	9 (11.8)
3	3 (3.9)
5	1 (1.3)
Liver cirrhosis, n (%)	28 (36.8)
HCV treatment-experienced (%)	20 (25.9)
SVR, n (%)	75 (97.4)
DAA treatment regimen [n (%)]	
Ombitasvir-paritaprevir-ritonavir + dasabuvir	31 (40.8)
Ombitasvir-paritaprevir-ritonavir + dasabuvir + ribavirin	9 (11.8)
Sofosbuvir + ledipasvir	14 (18.4)
Sofosbuvir + ledipasvir + ribavirin	7 (9.2)
Sofosbuvir + ribavirin	8 (10.5)
Glecaprevir + pibrentasvir	7 (9.2)

Results are expressed as median (IQR). The frequencies are expressed as number and percentage (%). SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis 4 score, HCV: Hepatitis C virus, IQR: Interquartile range, DAA: Direct-acting antiviral, SVR: Sustained virologic response

Baseline Mean Values Detected in APRI and FIB-4 Scores in Patients with Cirrhosis and Non-cirrhosisThe APRI and FIB-4 index exhibited significant statistical differences between patients with and without cirrhosis (7). Baseline APRI and FIB-4 scores of the patients with cirrhosis and non-cirrhosis are presented in Table 3.

At Baseline and EOT, the Scores of Non-invasive Tests (APRI, FIB-4)

At the end of the therapy, we observed significant decreases in APRI scores and and scores of FIB-4 [0.56 (0.30-1.06) vs. 0.24 (0.16-0.34), p<0.001; 2.20 (1.24-3.28) vs. 1.60 (0.85-2.15), p<0.001 respectively] significant decreases were observed.

End of Treatment, 1st Year, and 2nd Year After Treatment, Non-invasive Test Scores

At the EOT, 1st year after treatment, and 2nd year after treatment, we calculated the scores of APRI and FIB-4 in both groups, and the results are presented in Figures 1 and 2 by boxplot charts. Data is presented for cirrhotic patients in Table 4 and Figure 3. Data presented for non-cirrhotic patients on and Table 5 and Figure 4.We found a tendency to decline in the median scores of APRI and FIB-4 at follow-up based on EOT results (APRI, 0.49 vs. 0.41, p=0.87; FIB-4, 2.79 vs. 2.50, p=0.44), but there were no significant differences. However, cirrhotic patients had striking results after two years of follow-up. Both EOT 1& 2nd year APRI and FIB-4 in the cirrhotic patient [0.86 vs. 0.58, p<0.001; 4.74 vs. 3.59, p<0.001], as well as 1st and 2nd year APRI and FIB-4 [0.84 vs. 0.58, p=0.007; 4.74 vs. 3.59, p=0.004] had significant improvement. There was no statistically significant difference in non-cirrhotic patients at the two-year follow-up after EOT.

Table 2. Paired samples correlations all patients

		n	Correlation	p-value
ALT	Pre-treatment ALT & EOT ALT	75	0.243	0.036
AST	Pre-treatment AST & EOT AST	75	0.351	0.002
PLT	Pre-treatment PLT & EOT PLT	75	0.804	0.000

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, EOT: End of treatment, PLT: Platelet

Table 3. Baseline mean APRI and FIB-4 scores in cirhosis vs. non-cirhosis groups

Variables	Cirrhosis (28 patients)	Non-cirrhosis (48 patients)	p-value
APRI mean	2.39	0.81	<0.0001
FIB-4 mean	7.22	2.50	<0.0001

APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4 score. Results are expressed as mean value. Statistical significance of the differences between the cirrhotic patientsand non-cirrhotic patients was determined by p<0.05 using the independent samples t-test

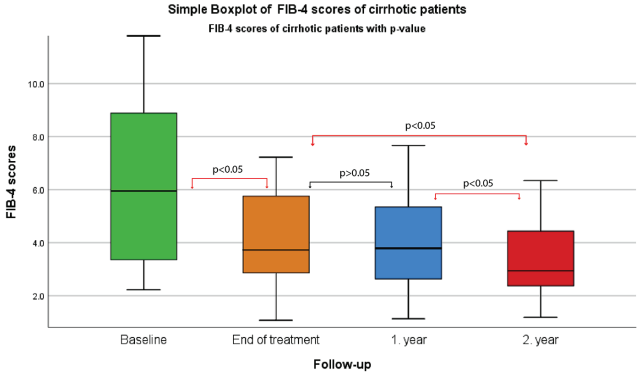

Figure 1. Follow-up plotbox diagrams of 1st year and 2nd year after treatment, FIB-4 scores of cirrotic patients

FIB-4: Fibrosis-4 score

DISCUSSION

Since the prognosis after treatment is mainly determined by the fibrosis stage, it is essential to assess whether fibrosis regression can be achieved after the completion of DAA therapy.

It has been shown that more fewer undesired conditions like liver cirrhosis, hepatic decompensation, and HCC are observed in patients with CHC who gained SVR than in those without SVR (11). However, the elimination of hepatic adverse events could not be warranted with SVR because these patients should receive post-SVR surveillance. In patients who have SVR, the residual liver fibrosis stage can predict adverse events in the liver (12). This study adds valuable data to the available literature through data from extended follow-up periods and comparative results, which might lead to better clarification to interpret the changes in the liver after treatment. It is one of the few studies observing changes in liver fibrosis screened with non-invasive tests over two years at specified time points of APRI and FIB-4 computation and comparing derived data before and after DAA treatment. Study outcomes were interpreted as follows; an improvement in liver fibrosis screened with NIT's between baseline and EOT might be associated with the resolution of inflammation soon after starting DAA therapy, whereas improvement over two years after treatment completion is more likely to represent a regression in liver fibrosis.

Our Pre-treatment and Post-treatment Results

In both cirrhotic and non-cirrhotic liver disease, significant regression was observed in screened fibrosis levels calculated using reliable non-invasive markers, regardless of the initial fibrosis stage after DAA therapy.

Table 4. Follow up APRI and FIB-4 scores for cirrhotic patients

Variables	EOT vs. 1 year post-EOT (26 patients)			EOT vs. 2 year post-EOT (23 patients)			1 year vs. 2 year post-EOT (23 patients)		
	EOT	1 year post-EOT	p-value	EOT	2 year post-EOT	p-value	1 year post-EOT	2 year post-EOT	p-value
APRI	0.86	0.84	0.905	0.86	0.58	0.000	0.84	0.58	0.007
FIB-4	4.74	4.62	0.878	4.74	3.59	0.000	4.62	3.59	0.004

APRI: Aspartate aminotransferase to platelet ratio index, FI-4: Fibrosis-4 score, EOT: End of treatment

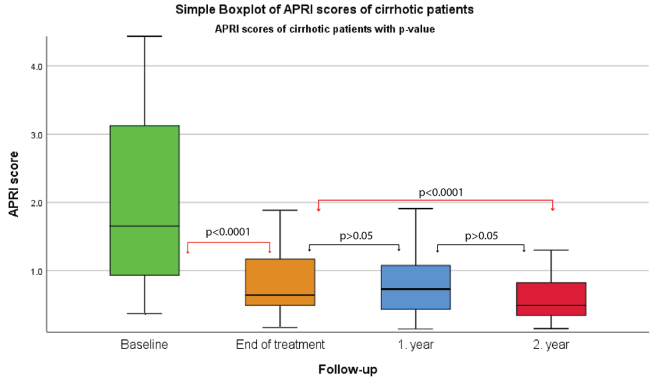

Figure 2. Follow-up plotbox diagrams of 1st year and 2nd year after treatment, APRI scores of cirrotic patients
APRI: Aspartate aminotransferase to platelet ratio index

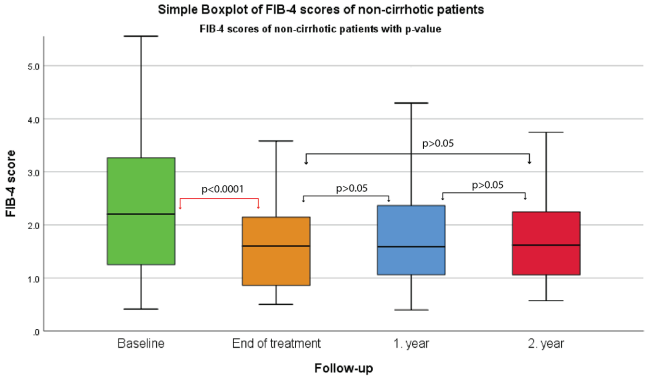

Figure 3. Follow-up plotbox diagrams of 1st year and 2nd year after treatment, FIB-4 scores of non-cirrotic patients
FIB-4: Fibrosis-4 score

Non-invasive tests (APRI, FIB-4 index) exhibited significant statistical differences between patients with and without cirrhosis (13). In recent studies, a remarkable decrease in hepatic enzymes and improvement in biochemical profile have been reported after DAA treatment (14,15). By Zhang et al. (16) comparing pre-treatment and EOT, ALT, AST, and platelet results, significant decreases were found (p=0.036, p=0.002, p=0.000, respectively). After SVR, a favorable improvement in hematological parameters (particularly platelets) has been reported. Changes in APRI and FIB-4 scores may be related to the rapid decline in hepatic

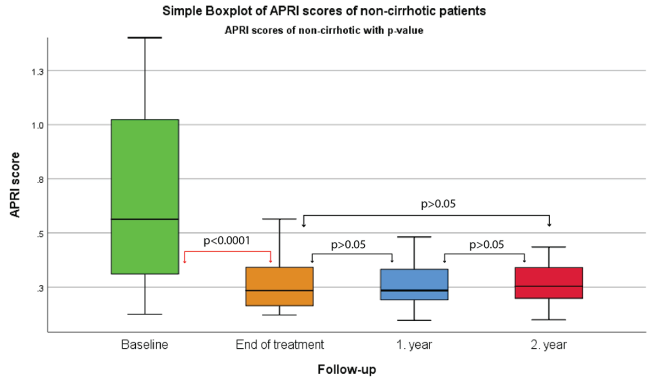

Figure 4. Follow-up plotbox diagrams of 1st year and 2nd year after treatment, APRI scores of non-cirrotic patients
APRI: Aspartate aminotransferase to platelet ratio index

transaminases (AST, ALT) and increase in platelets, mainly due to improvement in necroinflammation. However, this rapid regression achieved at the EOT may only reflect necroinflammatory resolution rather than actual fibrosis regression, leading to an overestimation of fibrosis regression.

Our Results of the EOT and One-year Post-EOT

We analyzed the EOT results of patients with and without cirrhosis, the 1st and 2nd-year APRI and FIB-4 scores, to reduce the confounding effect of the improvement in fibrosis scores necroinflammatory healing on liver fibrosis measurements in ongoing follow-ups.

Our Results of the EOT and Two-year Post-EOT

Impressive results were obtained in NIT's screening fibrosis regression at the 2nd-year follow-up in the cirrhotic patient group. In comparative computing of the EOT and two-year post-EOT scores of APRI (p=0.007) and FIB-4 (p=0.004), significant differences were found.

Most of the studies performed were performed shortly after the EOT (12 and 24 weeks) (17-19). The resolution of inflammation could be the primary reason of timely improvement; on the other hand, continued regression one year after EOT may be due to fibrosis reduction, as observed in liver biopsy studies paired with interferon-

Table 5. Follow-up APRI and FIB-4 scores for non-cirrhotic patients

Variable	EOT vs. 1 year post-EOT (46 patients)			EOT vs. 2 year post-EOT (39 patients)			1 year vs. 2 year post-EOT (39 patients)		
	EOT	1 year post-EOT	p-value	EOT (48 patients)	2 year post-EOT	p-value	1 year post-EOT	2 year post-EOT	p-value
APRI	0.28	0.29	0.909	0.28	0.26	0.313	0.29	0.26	0.312
FIB-4	1.71	1.86	0.259	1.71	1.86	0.306	1.86	1.89	0.315

APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4 score, EOT: End of treatment

based therapy (20,21). Prakash and Rockey (22) showed that 39% of cirrhotic patients had a reduction of <2.67 in the FIB-4 monitoring technique.

A recent systematic review of 24 observational studies with another invasive fibrosis assessment method that is vibration- controlled transient elastography, showed a significant early reduction in liver stiffness followed by a milder decrease one year later in patients with HCV infection (who acquired SVR), by Singh et al. (23).

Our post-EOT 2-year follow-up results; although the 1st year NIT's screened fibrosis regression was insignificant in cirrhotic patients with a high fibrosis score, in the second year, fibrosis reduction continued and became significant in this group.

Limitations of the study. First, we had no histological examination was to observe correlations with transitory variance in non-invasive fibrosis parameters of patients while taking and after DAA treatment. Second, there was a scarce number of patients since it was a single-center study. Since it was a small cohort, we could not statistically determine additional patient factors independently associated with significant improvement in fibrosis scores.

CONCLUSION

The study adds important and detailed data to the literature by revealing a continuous improvement in NIT's screened for liver fibrosis two years after EOT. Although long-term fibrosis regression was more limited than observed rapid decreases at EOT, this finding is significant when considering cirrhosis and advanced fibrosis regression, which is a slow process requiring long-term follow-up.

Multi-centre clinical studies with a larger dataset will allow more detailed and robust statistical and clinical data to reveal long-term treatment responses.

ETHICS

Ethics Committee Approval: The study was approved by the Ethics and Clinical Research Committee of the University of Health Sciences Türkiye, Haseki Training and Research Hospital (decision no: 27-2022, date: 16.02.2022). The research conforms to the provisions of the Declaration of Helsinki in 1995.

Informed Consent: Retrospective study.

Authorship Contributions

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

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

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Research

Clinical Features of Children and Adolescents at the Onset of Diabetes: A Single-center Experience

Diyabetli Çocuk ve Ergenlerin Tanıdaki Klinik Özellikleri: Tek Merkez Deneyimi

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ABSTRACT

Objective: This study evaluated the findings of pediatric cases with diabetes mellitus (DM) who were admitted to a pediatric endocrinology unit for two years.

Methods: In this retrospective, observational study, children and adolescents aged 0-18 years, were diagnosed with DM were evaluated. Cases were grouped as formerly diagnosed and new-onset. Demographic and laboratory features at admission were recorded. The type of diabetes was classified and, also the presence of diabetic ketoacidosis (DKA) and severe DKA was described according to the current criteria.

Results: The mean age of 108 children (51 girls) at the time of the first evaluation in our unit was 10.3±4.4 (range 0.7-17.9) years. Seventy-eight children were diagnosed with diabetes (new-onset group) during the study period. The median age of the new-onset group was 11.2 years (IQR:6.3-13.1) The distribution of, type 1 diabetes (T1D), type 2 diabetes (T2D), and monogenic diabetes was 79.5% (n=62), 7.7% (n=6), and 12.8% (n=10), sincerely. The distribution of the types was similar in the formerly diagnosed group and the new-onset group (p=0.899). Sixty-two cases (28 girls) with new-onset T1D were evaluated. The mean age was 9.3±4.6 years (range 0.7-17.9) and, twenty-one percent of them (n=13) were under 5 years of age. The rate of DKA at the presentation was 41.9%. Severe acidosis (pH<7.1) ratio was 19.4%, and the percentage of cases with HCO_3<5 mmol/L was 1.6%. Under 5 years of age, the ratio of acidosis and severe acidosis was higher than the cases older than 5 years (69.2% vs 34.7%, p=0.032 and 46.2% vs. 12.2%, p=0.013, sincerely).

Conclusion: In our study, the rate of monogenic diabetes was found to be higher. In the widespread use of high-throughput genetic techniques era, the diagnosis will change to monogenic diabetes in antibody-negative children followed up with the diagnosis of type 1 diabetes. The rate of DKA has remained unchanged for 40 year; this fact indicates that striking and continuous programs targeting increased awareness of diabetes are needed.

Keywords: Diabetes mellitus, type 1 diabetes, type 2 diabetes, MODY, diabetic ketoacidosis

ÖZ

Amaç: Bu çalışmada, çocuk endokrinoloji ünitesine iki yıllık dönemde başvuran diabetes mellitus (DM) tanılı pediatrik olguların bulgularının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Retrospektif, gözlemsel olarak planlanan çalışmada 0-18 yaş arası DM tanısı alan çocuk ve ergenler değerlendirildi. Olgular, önceden tanı almış ve yeni tanı olarak gruplandırıldı. Başvuru anındaki demografik ve laboratuvar özellikleri kaydedildi. Diyabet tipi ve diyabetik ketoasidoz (DKA) ve şiddetli DKA varlığı güncel kriterlere göre belirlendi.

Bulgular: Kliniğimizde değerlendirilen 108 çocuğun (51 kız) yaş ortalaması 10,3±4,4 yıl (aralık 0,7-17,9) idi. Olguların 78'ini çalışma döneminde tanı alan yeni tanı diyabetler oluşturdu. Yeni tanı diyabet olgularının ortanca yaşı 11,2 yıl idi (IQR:6,3-13,1). T1D, T2D ve monogenik diyabet dağılımı sırasıyla %79,5 (n=62), %7,7 (n=6) ve %12,8 (n=10). Diyabet tipi dağılımı önceden tanı almış grup ile yeni tanı alan grupta benzerdi (p=0,899). T1D'li 62 olgu (28 kız) değerlendirildi. Yaş ortalaması 9,3±4,6 yıl (aralık 0,7-17,9) idi. Beş yaşın altındaki olgu oranı %21 (n=13) idi. Başvuruda DKA oranı %41,9 idi. Şiddetli asidoz (pH<7,1) oranı %19,4, HCO_3<5 mmol/L olan olguların yüzdesi ise %1,6 idi. Beş yaş altında asidoz ve şiddetli asidoz oranı, beş yaş üstü olgulara göre daha yüksekti (sırasıyla %69,2 vs. %34,7, p=0,032; %46,2 ve %12,2, p=0,013).

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ÖZ

Sonuç: Bu çalışmada, monogenik diyabet oranı yüksek bulunmuştur. İleri genetik tekniklerin kullanılabilirliğinin artışı ile tip 1 diyabet tanısı ile izlenmekte olan antikor negatif olguların bazılarında monogenik diyabet tanısının konulabileceği düşünülmektedir. DKA oranının 40 yıldır değişmeden kalması, diyabet farkındalığını artırmaya yönelik çarpıcı ve sürekli programlara ihtiyaç olduğunu göstermektedir.

Anahtar Kelimeler: Diabetes mellitus, tip 1 diyabet, tip 2 diyabet, MODY, diyabetik ketoasidoz

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic and multisystemic condition that occurs due to insulin deficiency and/or insufficiency in insulin action. American Diabetes Association (ADA) classifies DM as, type 1 diabetes (T1D) (usually absolute insulin deficiency due to autoimmune beta-cell destruction), type 2 diabetes (T2D) (non-autoimmune progressive loss of adequate insulin secretion frequently because of insulin resistance), specific types of diabetes due to other causes, and gestational diabetes mellitus. Specific types of diabetes include monogenic diabetes syndromes, diseases of the exocrine pancreas, and drug -or chemical-induced diabetes and other causes (1).

The most common form of DM in children is T1D, and its incidence varies between countries (2). The number of new-onset and existing T1D cases is increasing (3). Worldwide, over 1.2 million children and adolescents younger than 20 years are estimated to have T1D. Approximately 150,000 children and adolescents under 20 years old are diagnosed each year (4). In Turkey, the total prevalence of T1D in children under 18 years was reported to be 0.75/1,000 (5), and 0.67/1,000 in school-age children (6-18 year old) in İstanbul (6). There are nearly 20,000 children under 18 years old with existing T1D in Turkey (7). The reported mean incidence in the last decade varies between 7.2-16.7 per 100,000 (5,8-10). These epidemiological studies showed that Turkey is a country with an intermediate incidence rate compared to the rest of the world (8). It is possible to say that there is an increase in the frequency of T1D in Turkey; however, since epidemiological data are scarce, it is based only on clinical observations and regional studies in the last decade. In regional studies during the 2010s from the eastern part of Turkey, an increase in the incidence of T1D was reported (9,10).

Acute complications are the most important cause of mortality and morbidity in children with T1D. Diabetic ketoacidosis (DKA), is one of the acute complications and is more frequent in new-onset cases who have risk factors such as young age, lower socioeconomic status, and living in a region with a low prevalence of T1D due to delayed diagnosis (11). The diagnosis of T1D may be delayed until the hospital admission for DKA, sometimes with fatal results. DKA frequency at diagnosis of T1D in high-income countries had been reported approximately 30% before 2020 (12). However, frequencies range from 15% to 70% in Europe and North America when the studies during the coronavirus disease-2019 (COVID-19) pandemic are included (13). Reducing the frequency of DKA and especially severe DKA in diagnosis is essential in terms of mortality, morbidity, and the emotional status of the families at the onset of diabetes. Activities targeting increased awareness of diabetes symptoms among parents, school teachers, and healthcare professionals have been successful in reducing DKA frequency (14,15).

T2D and other specific types of diabetes are also diagnosed during childhood. Adolescence is the period that T2D occurs in the pediatric age group, accounting for 15-86% of new-onset diabetic cases in adolescence in the United States (US). This variable rate is due to a disproportionally high incidence in some ethnic groups. In non-Hispanic white youth and in Europe, these rates are reported to be lower (16). In addition to the increase in obesity, many genetic/epigenetic mechanisms are thought to play a role in the development of T2D. Monogenic diabetes syndromes are diabetes due to single -gene alterations, including cases defined as maturity-onset diabetes of the young (MODY) as well as neonatal DM (NDM) cases diagnosed in the first 6 months of life. The frequency of monogenic diabetes in childhood diabetes is reported as 1%-6% (17).

This study evaluated the findings of pediatric cases with diabetes who were admitted to our Pediatric Endocrinology Unit in İstanbul between 01.04.2015 and 31.03.2017 for two years.

METHODS

In this retrospective, observational study, 108 (51 girls) children and adolescents aged 0-18 years, who applied to the Pediatric Endocrinology Unit in University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital in İstanbul between April 1st, 2015, and March 31st, 2017, and were diagnosed with DM according to the ADA criteria (1), were evaluated.

Thirty cases (14 girls) were diagnosed at another unit before April 1st, 2015, and admitted to our unit for follow-up. These cases were grouped as formerly diagnosed.

Seventy-eight (37 girls) were diagnosed in our unit during the study period and were grouped as new-onset.

Demographic (age, gender) and laboratory features [glucose (mg/dL), c-peptide level (ng/mL), presence of autoantibodies including islet cell autoantibodies (ICA), glutamic acid decarboxylase antibodies (GADA) and insulin autoantibodies (IA), presence of ketone bodies in urine, venous pH, and HCO_3 levels (mmol/L)] at admission were recorded.

The presence of DKA was described due to both International Society for Pediatric and Adolescent Diabetes (ISPAD) 2018 (venous pH<7.25 or HCO_3<15 mmol/L) (11) and ISPAD 2022 (venous pH<7.25 or HCO_3<18 mmol/L) (13). Severe DKA was defined as venous pH<7.1 or HCO_3<3 mmol/L.

The type of diabetes was evaluated, and cases were classified according to the ADA criteria (1).

T1D was diagnosed in insulin-deficient cases with the presence of autoantibody positivity, and the absence of any suggestive signs of other causes of diabetes. The diagnostic criteria for T2D were based on overweight/obesity, clinical findings of insulin resistance (acanthosis nigricans), family history of T2D, and good metabolic control with metformin or metformin combined with low-dose insulin. Children who had a family history of diabetes or specific findings such as deafness, optic atrophy, or renal cysts with negative autoantibodies and cases with an onset of diabetes younger than 6 months of age (NDM) were classified as clinically monogenic diabetes. The results of molecular genetic tests such as next-generation sequencing (NGS) that were performed on these cases were also recorded.

Statistical Analysis

Were performed using the statistical package for the social sciences software version 15 (LEAD Technologies Inc, 2006). Data were presented with n (%) for categorical data and mean ± standard deviation for numerical data. Chi-square tests were used for the comparison of categorical data (Fisher's exact test was used when chi-square test assumptions do not hold due to low expected cell counts). In the comparison of the independent 2 groups, the student t-test was used if the data were normally distributed, and the Mann-Whitney U test was used if the data were non-normally distributed. Type 1 error was determined as 5%, and a p-value <0.05 was considered statistically significant.

The study was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (ATADEK) (decision no: 2018-20/35, date: 20.12.2018). The study was retrospective and did not involve interventions; thus, informed consent from the parents and cases was not obtained. A consent waiver for this study was obtained from the ethics committee.

RESULTS

The mean age of 108 children (51 girls) at the time of the first evaluation in our unit was 10.3±4.4 (range 0.7-17.9) years. At diagnosis, 21.3% of the cases were younger than 5 years, and 55.6% of the cases were older than 10 years. Eighty-seven were diagnosed with T1D (80.6%), eight with T2D (7.4%), and 13 with monogenic diabetes (12.0%). The ratio of T2D in cases older than 10 years at diagnosis was 13.3%. The distribution of the cases are summarized in Figure 1.

Formerly Diagnosed Cases

Thirty children (14 girls) were diagnosed before the study period at another unit and admitted to our unit for follow-up. The median age of those at the onset of diabetes was 7.1 years ranging between 0.1 and 15.1 years The median duration of diabetes was 2.3 years. In this group, the distribution of T1D, T2D, and monogenic diabetes was 83.3% (n=25), 6.7% (n=2), and 10.0% (n=3), sincerely.

In the monogenic diabetes group, there was only one case (Case#91) with NDM, diagnosed on the postnatal 18th day. She had KCNJ11-NDM and had been switched to sulfonylurea (SU) (glibenclamide) in infancy, and was admitted first to our unit at the age of 4.1 years.

A case in this group, an 11-year-old girl (C#93), had been diagnosed with T1D at the age of 6 years. She had been treated with multiple daily injections (insulin lispro and glargine, total insulin 0.8 U/kg per day). GADA and ICA were negative. Her mother was also diagnosed with diabetes at the age of 14 years, the duration of her diabetes was 23 years, and she had severe microvascular complications such as retinopathy. There were many individuals with diabetes in their family; therefore, NGS panel for MODY was performed. In the *hepatocyte nuclear factor 1-α (HNF1A)* gene, a heterozygous frameshift variant (c.1853_1854delTC, p. Ile618Argfs*30) was detected both in C#93 and her mother. After the genetic diagnosis of HNF1A-MODY was established in these cases, transfer from insulin therapy to glibenclamide was attempted. In the girl, insulin requirement decreased, and insulin therapy ceased; however, the mother had no response to SU.

New-onset Cases

Seventy-eight children (37 girls) were diagnosed with diabetes in our unit during the study period. The median age of the new-onset group was 11.2 years (IQR25-75 6.3-

13.1) (mean age 9.9±4.4 years, range 0.7-17.9). In the new-onset group, the distribution of, T1D, T2D, and monogenic diabetes were 79.5% (n=62), 7.7% (n=6), and 12.8% (n=10), sincerely. The distribution of the types was similar in the formerly diagnosed group and the new-onset group (p=0.899).

Sixty-two cases (28 girls) with T1D were evaluated. The mean age was 9.3±4.6 (range 0.7-17.9). Twenty-one percent of them (n=13) were under 5 years of age. Only one case (C#74) was under 12 months of age. She was 8.7 months old at the onset of diabetes and had severe DKA, and three autoantibodies were positive.

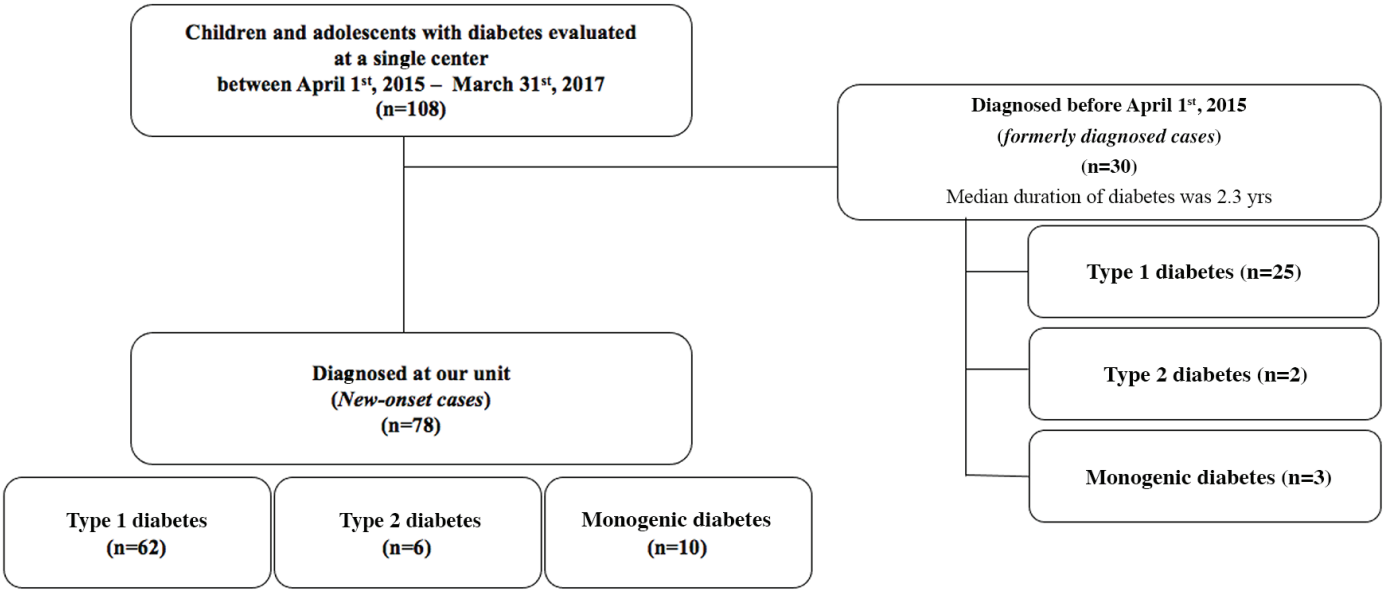

Figure 1. Distribution of cases according to the types of diabetes

Table 1. Features of children and adolescents with type 1 diabetes in the new-onset group

	Ketoacidosis (-)	Ketoacidosis (+)	All	p
Girls, n (%)	17 (42.3)	11 (47.2)	28 (45.2)	0.701
Age (years)	10.0±4.4	8.2±4.7	9.3±4.6	0.116
Age <5 years, n (%)	4 (11.1)	9 (34.6)	13 (21.0)	0.032
Glucose (mg/dL) mean ± SD	449.5±161.2	496.0±133.4	468.9±150.8	0.236
C-peptide (ng/mL) mean ± SD median	1.1±0.7 0.9	0.5±0.4 0.4	0.9±0.7 0.8	0.004
Ketonuria (+) n (%)	27 (75.0)	26 (100.0)	53 (85.5)	0.008
pH mean ± SD	7.37±0.05	7.11±0.11	7.26±0.15	<0.001
HCO_3 (mmol/L) mean ± SD	22.2±3.0	9.0±3.3	16.6±7.3	<0.001
GADA (+), n (%)	20 (62.5)	17 (68.0)	37 (64.9)	0.666
ICA (+), n (%)	21 (65.6)	20 (80.0)	41 (71.9)	0.231
IA (+), n (%)	4 (14.8)	6 (31.6)	10 (21.7)	0.277
Antibody (+), n (%)	25 (75.8)	24 (96.0)	49 (84.5)	0.064
Antibody (-), n (%)	7 (21.9)	1 (4.0)	8 (14.0)	0.067
Two or more antibodies (+), n (%)	19 (59.4)	15 (65.2)	34 (61.8)	0.660

GADA: Glutamic acid decarboxylase antibodies, ICA: Islet cell autoantibodies, IA: Insulin autoantibodies, SD: Standard deviation

The DKA-2018 (pH<7.30 or HCO_3<15.0 mmol/L) ratio at presentation was 41.9%. The percentage of cases with DKA-2022 (HCO_3<18 mmol/L) was 50.0%. Severe acidosis (pH<7.1) ratio was 19.4%, and the percentage of cases with HCO_3<5 mmol/L was 1.6%. Under 5 years of age, the ratio of acidosis and severe acidosis was higher than the cases older than 5 years (69.2% vs. 34.7%, p=0.032 and 46.2% vs. 12.2%, p=0.013, sincerely). Laboratory features of the cases with T1D are given in Table 1.

In 58 cases with T1D, at least one autoantibody level was tested. Seventy-nine percent of those had at least one positive antibody. Two or more antibodies were positive in 34 cases (54.8%). The ratio of cases with negative antibodies among the cases that were tested for at least two antibodies was 12.9% (n=8). A comparison between two-antibody-positive (n=34) and antibody-negative (n=8) cases in terms of median age, pH, and HCO_3 levels was performed. The median age, pH, and HCO_3 levels in these groups were 10.5 vs. 13.0 years (p=0.289), 7.30 vs. 7.39 (p=0.060), and 17.8 vs. 22.6 mmol/L (p=0.06), sincerely. The percentage of presence of urinary ketones was also similar in these groups (79.4% vs. 87.5%, p>0.05).

In the new-onset group, six cases (7.7%) were diagnosed with T2D. All of these cases were older than 10 years (range 10.4-15.3 years) and had body mass index (BMI) higher than 95 gentiles. No ketone body and no DKA were detected. All the three autoantibodies were negative in these cases. The frequency of T2D (n=6) among cases older than 10 years (n=47) was 12.8%.

Among the 10 cases with monogenic diabetes, seven cases were [Glucokinase (GCK)-MODY], and 5 of them had a result of a molecular genetic test compatible with the diagnosi; however, 2 of them only had a clinical diagnosis of GCK-MODY.

In the other monogenic diabetes cases (n=3), two cases (C#40 and C#47) with negative autoantibodies and with a strong family history, monogenic diabetes were clinically diagnosed. Unfortunately, molecular genetic tests in these cases could not be performed. The third case, a 14.8-year-old male adolescent (C#53), had a confirmed molecular diagnosis of [hepatocyte nuclear factor-1β (HNF1B)-MODY]. He had no known disease before and was admitted to our clinic with a complaint of polydipsia for a month. He was born at term with a weight of 2,750 g. There were no consanguinity and no family history of diabetes or kidney disease. His height and BMI standard deviation score were +1.0 and -0.7, sincerely. Systemic examination was normal, Tanner stage 5, and pectus excavatum was noticed. Serum glucose, urea, and creatinine were elevated (glucose 822 mg/dL, urea 62 mg/dL, and creatinine 1.49 mg/dL). Trace ketonuria without DKA was detected (venous pH 7.37 and HCO_3 26.7 mmol/L). Glycosylated hemoglobin (HbA1c) was 12.2%, and the c-peptide level was 0.87 ng/mL. Appropriate intravenous fluid and insulin therapy were initiated for severe hyperglycemia and high creatinine levels. Although euglycemia and normal hydration was achieved, a slightly elevated creatinine level persisted. Ultrasonography revealed increased echogenicity of the renal parenchyma and two cysts of 1 cm in diameter in the left kidney. An increase in the transaminase level was observed. GADA, ICA, and IA were found to be negative, and in the *HNF1B* gene c.827G>A, p. Arg276Gln, a missense heterozygous mutation was detected. His parents were negative for the variant.

All Cases

Overall, the ratio of monogenic diabetes was 12.8%. However, 6 (7.7%) of them had confirmed molecular etiology. The ratio of monogenic diabetes by excluding GCK-MODY cases and was found to be 4.3%.

Apart from these cases of monogenic diabetes, in our cohort, there were 8 cases with negative autoantibodies. In six of them with a classical presentation, without obesity, and without a negative family history, the T1D diagnosis was almost determined. However, in 2 cases with three negative autoantibodies, the type of DM could not be determined. In C#40, a 14.5-year-old girl, presenting with obesity, and trace ketonuria, without DKA, had an HbA1c level of 14.4%. She had a strong family histor; however, no variant was detected in the MODY gene panel with NGS. In C#59, a 14.9-year-old girl with obesity had intellectual insufficiency and she presented without DKA. A c-peptide level of 2.49 ng/mL was found, while her glucose level was 274 mg/dL.

All cases with monogenic diabetes in the formerly diagnosed and new-onset groups are given in Table 2.

DISCUSSION

In this study, we presented our pediatric diabetes cohort from a newly established center in İstanbul. There are many similar studies from Turkey (18,19); however, most of them are either from tertiary centers in high-populated provinces or from centers in relatively-low-populated provinces. This study differs from previous studies since it is from a non-tertiary center in a high-populated province. Additionally, we think that it is necessary to continue these audit studies in terms of the trends in the changing characteristics of children with diabetes.

Table 2. Clinical and genomic features of cases with monogenic diabetes

# Case	Age at diagnosis, gender	Family members with diabetes	Glucose mg/dL, ketone	HbA1c (%)	Acidosis	Ab	Gene	Variant zygosity
27	11.0, M	Sister (C#30), father, uncle, grandfather	142, negative	6.6	-	+ GADA	*GCK*	c.46-2A>G heterozygous
30	15.1, F	Brother (C#27), father, uncle grandfather	129, negative	6.7	-	-	*GCK*	c.46-2A>G heterozygous
40	15.2, F	Sister, mother, grandmother	343, positive	15.9	-	-	*N/A*	-
47	12.4, F	Father, grandmother	229, negative	11.5	-	-	*N/A*	-
53	14.8, M	No family history of diabetes	822, trace	12.2	-	-	*HNF1B*	c.827G>A p.Arg276Gln heterozygous
55	11,4, F	Brother, mother, aunt	131, negative	6.1	-	-	*GCK*	c.1226A>C p.Asp409Ala heterozygous
58	11.6, M	Father, grandfather	142, negative	N/A	-	-	*GCK?*	N/A
60	13.4, F	Mother, grandfather	126, negative	N/A	-	-	*GCK?*	N/A
70	5.1, M	Father	127, negative	N/A	-	-	*GCK*	c.1256G>C p.Arg422Pro heterozygous
72	11.3, F	N/A	130, negative	6.6	-	-	*GCK*	c.227C>T p.Ser76Phe heterozygous
91	0.1, F	No family history of diabetes	N/A	N/A	N/A	N/A	*KCNJ11*	c.155A>T p.Gln52Leu heterozygous
93	6.0, F	Mother, aunts, uncles	170, negative	6.7	-	-	*HNF1A*	c.1853_1854delTC p.Ile618Argfs*30 heterozygous
97	14.5, M	No family history of diabetes	519, negative	14.6	-	-	*WFS1*	c.2206G>A p.Gly736Ser homozygous

F: Female, M: Male, *HNF1A: Hepatocyte nuclear factor 1-α, GCK: Glucokinase, HNF1B: Hepatocyte nuclear factor-1β*

The distribution of types of DM differs due to many factors. In Caucasians, T1D constitutes by far the majority (over 90%) of childhood diabetes (2). Overall in our cohort, the T1D ratio was 80.6%. Although similar to previous studies, T1D is the most common, the percentage is lower. Considering that there may be a bias regarding the application of formerly diagnosed patients, this rate was also evaluated in cases diagnosed in the study period at our center (new-onset cases) and a similar result was found (79.5%). As can be seen, 1/5 of the cases were not T1D. The reason for this high rate of non-T1D cases is explained by the high frequency of monogenic diabetes (approximately 12.8%) in our cohort, which is commonly reported in different studies as 1%-6% of childhood diabetes (17). There are two considerable factors in determining this high rate in our cohort. The first one may be that possible cases without molecular genetic confirmation were also included in the monogenic diabetes group. The ratio was 7.7% if only cases with confirmed molecular etiology were included. However, we believe that the cases without detectable variants would be confirmed with the increased availability of high-throughput genetic testing such as whole-exome sequencing. For this reason, we think that the accepted rates (1%-6%) for monogenic diabetes belong to the periods when the accessibility

of molecular genetic tests was insufficient. Today, the main criteria for genetic testing in diabetes are negative-autoantibodies and having a strong family history (1). Because of the autosomal dominant inheritance pattern of the disease, antibody-negative atypical cases without a family history should also be included in genetic testing due to possible *de novo* variants as we detected in our case with HNF1B-MODY. Apart from these cases that we determined to have monogenic diabetes in our cohort, there were eight more cases with negative autoantibodies. In six of them with a classical presentation, without obesity, and without a negative family history, the T1D diagnosis was almost determined. However, in two cases with three negative autoantibodies, the type of DM could not be determined. In a recent study from Finland (20), more than 10% of antibody-negative children with diabetes were found to be a genetic variant and diagnosed with monogenic diabetes regardless of the family history of diabetes. We believe that, as high-throughput genetic tests become easily available, the rate of monogenic diabetes in children will reach over 10%, at least in countries with an intermediate incidence of T1D.

The second factor for the high rate of monogenic diabetes would be the low threshold for testing the GCK variants in mild fasting hyperglycemia. GCK-MODY presents with a different clinical picture from typical childhood diabetes, and in many cohorts, mild cases would not be included. Therefore, we calculated the rate of monogenic diabetes in our cohort also by excluding GCK-MODY cases and found it to be 4.3%. Recent publications have reported that GCK-MODY is the most common type of monogenic diabetes (21,22). Detecting pathogenic *GCK* gene variants in cases with fasting hyperglycemia would prevent unnecessary treatment in cases misdiagnosed with T2D (1,17). Additionally, some of these cases with GCK-MODY are being followed closely with the diagnosis of prediabetes, and this could be over.

The most important consequences of determining of the diagnosis of monogenic diabetes are genetic counseling and detection of other accompanying conditions, as in our case with HNF1B-MODY. Additionally, as in the cases of HNF1A-MODY, and KCNJ11-NDM in our cohort, the chance of change in treatment is very striking in childhood diabetes.

The frequency of childhood T2D has increased dramatically in North America, especially in ethnic minority populations (23). While the frequency of T2D in children is increasing in the US (24), this ratio is still lower in Europe (1.3%) (25). In a single-center study in İstanbul (18), it was reported that 5.7% of childhood diabetes diagnosed between 1999 and 2016 and 11.8% of children older than 10 years were T2D. It was also shown that there was a significant increase in the frequency of T2D among all DM between 2011 and 2016 compared to previous years. The rate of T2D in children over the age of 10 between 2011 and 2016 was 16% (18). In our cohort, 7.7% of the cases were diagnosed with T2D. All of these cases had obesity, and all were older than 10 years. The frequency of T2D among cases older than 10 years was 12.8%. No ketone body and no DKA were detected. All three autoantibodies were negative in cases with T2D in our cohort. T1D and T2D are heterogeneous disorders, and some cases cannot be clearly classified at the onset of DM (1). In our cohort, cases with their typical features were easily diagnosed with T2D. Although the positive autoantibodies are mostly related to T1D, up to 15% of the cases with T2D had positive autoantibodies (18,26). Also, cases with T2D may rarely present with DKA, and the expected glucose levels at presentation are mostly lower than the cases with T1D (<360 mg/dL) (1,27).

Immune-mediated diabetes diagnosed with autoantibodies include ICA, GADA, IA, and tyrosine phosphatases islet antigen 2 (IA-2) and IA-2b, and zinc transporter 8 (ZnT8) are important in the classification of diabetes in children. In our cohort, 58 cases with T1D, at least one autoantibody level was tested. One of the clinical limitations in our routine practice is that IA-2, IA-2b, and ZnT8 antibodies cannot be tested. Seventy-nine percent of those had at least one positive antibody. Two or more antibodies were positive in 54.8%. The ratio of cases with negative antibodies among the cases that were tested for at least two antibodies was 12.9%.

The second outcome of our study is the DKA frequency in T1D. DKA is the foremost morbidity and mortality cause of T1D. The frequency of the DKA in our new-onset T1D cohort was presented both due to ISPAD-2018 (11) and ISPAD-2022 (13), 41.9% and 50.0%, sincerely. The severe acidosis (pH<7.1) ratio was 19.4%. However, mostly we used HCO_3<5 mmol/L criteria for the definition of severe acidosis in our clinical practice, and the ratio of these cases was 1.6%.

Recently, a comprehensive review of the DKA rate in children with T1D covering almost all studies from Turkey over 40 years by Esen and Okdemir (19) was published. The rate of DKA at the onset of DM was reported as 45.6% in 8837 children. The limitations of this review were that the designs of the studies included in this review were heterogeneous and that only the abstracts of some studies have been evaluated. As seen in this review, apart from the periodical and regional small differences between the studies, by 2019, there was no change in the rate of DKA in Turkey for the last 40 years (19). In our cohort, the frequency of DKA at the onset of DM was similar.

Programs targeting increased awareness of diabetes symptoms among parents, school teachers, and, healthcare professionals have been successful in reducing DKA frequency (14,15). In Turkey by the 2010s, childhood diabetes program activities (7,28) have been carried out. Although a positive effect of these programs on the DKA rate at the onset of DM was reported in a study (29), it is seen that this study had showed an acute effect of the program since it was carried out in the next year of the program. This effect was not demonstrated by later studies (19) due to the limited memory of the community in the long term. Awareness again decreased and the frequency increased to similar levels. It would be beneficial to conduct continuous programs, especially to reduce severe acidosis.

In our cohort, in young cases (<5 years), DKA and severe DKA rates were significantly found to be higher. The risk of DKA at the onset of T1D is greater in younger children due to the difficulty in recognizing the symptoms of diabetes. While in some studies, no difference was reported in DKA rate due to age groups, some studies as our cohort found that the frequency of DKA was higher in children (19). A relationship between DKA risk and being younger than 5 years was shown by Uçar et al. (29).

In our cohort, no gender difference was found between cases presented with DKA and without DKA during the onset of T1D. The effect of gender on the DKA rate was evaluated in a meta-analysis (30), and no effect was detected. In Turkey, studies reported different DKA rates in terms of gender. In the two largest cohorts evaluating the long-term experience of centers, DKA rates at the onset of T1D were reported to be higher in girls (31,32). In subsequent studies, it was observed that there was no gender difference (19).

After COVID-19, increased rates of DKA at the onset of T1D were reported from six centers in Turkey. These six studies all together showed that while the DKA rate 42.3% in the 2018-2020 period before COVID-19, it was increased to 59.3% between 2020 and 2022 during the COVID-19 period (33-38). The reasons for the increase were attributed to the decrease in the awareness of other diseases due to the severe COVID-19 clinic and delays in admission to the hospital.

CONCLUSION

The rate of monogenic diabetes was found to be higher in our study. In the widespread use of high-throughput genetic techniques era, the diagnosis will change to monogenic diabetes in antibody-negative children followed up with the diagnosis of T1D. The rate of DKA has remained unchanged for 40 year; this fact indicates that striking and continuous programs targeting increased awareness of diabetes are needed.

ETHICS

Ethics Committee Approval: The study was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (ATADEK) (decision no: 2018-20/35, date: 20.12.2018).

Informed Consent: The study was retrospective and did not involve interventions; thus, informed consent from the parents and cases was not obtained.

Authorship Contributions

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

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Research

Retrospective Evaluation of P-wave Dispersion on ECG in Terms of Atrial Fibrillation Dispersion in Patients Using Alpha-blockers for Lower Urinary Tract Symptoms

Alt Üriner Sistem Semptomları Nedeni ile Alfa-bloker Kullanan Hastalarda EKG'de P-dalga Dispersiyonunun Atriyal Fibrilasyon Dispersiyonu Açısından Retrospektif Olarak Değerlendirilmesi

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ABSTRACT

Objective: The incidence of benign prostatic hyperplasia (BPH) directly increases with age, and side effects related to drugs in the alpha-blocker group used in these patients are more important. In this study, we evaluated the safety of tamsulosin in cardiac arrhythmias, which are common in this age group.

Methods: Between May and June 2017, 835 patients with BPH were evaluated retrospectively. Patients with cardiovascular and endocrine system diseases were excluded from the study. Tam In 55 patients who met the study criteria, tamsulosin was started as BPH treatment. Moreover, a control group was formed with patients who had not on tamsulosin treatment yet. Electrocardiographies (ECGs) of 37 patients who completed 3 weeks of tamsulosin use were obtained. Control and reference P-wave distribution (PWD) were calculated for each patient. The difference between the largest and narrowest p-waves on the ECG was calculated to determine the PWD. PWD values before and after treatment were compared.

Results: The mean age was 53.6±8 years. PWD values in reference and control ECG were calculated and compared. While the mean PWD was 55 ms (30-75) before tamsulosin use, it was 60 ms (45-70) 3 weeks after tamsulosin use.

Conclusion: PWD change in ECG was found to be significant in patients with BPH patients treated with tamsulosin. According to the results, I an increase in PWD is a finding that indicates an increased risk of supraventricular tachycardia. Therefore, the clinician should be more careful when using tamsulosin in these patients.

Keywords: Alpha-blocker, arrhytmogenic, benign prostate hyperplasia

ÖZ

Amaç: Benign prostat hiperplazisinin (BPH) insidansı yaşla birlikte doğrudan artmaktadır ve bu hastalarda kullanılan alfa-bloker grubundaki ilaçlara bağlı yan etkilerin sonuçları daha kritik olabilmektedir. Bu nedenle, bu çalışmamızda, BPH tedavisi alan yaş grubunda sık görülen kardiyak aritmiler açısından, alfa-bloker olarak tamsulosin kullanarak tedavinin güvenirliliğini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Mayıs-Haziran 2017 tarihleri arasında BPH şikayeti olan 835 hasta retrospektif olarak değerlendirildi. Kardiyovasküler ve endokrin sistem hastalığı olanlar çalışmaya alınmadı. Çalışma kriterlerine uyan 55 hastaya tamsulosin başlandı. Üç haftalık tamsulosin kullanımını tamamlayan 37 hastanın elektrokardiyografileri (EKG) çekildi. Her bir hasta için kontrol ve referans P-dalga dağılımı (PWD) hesaplandı. PWD, EKG'deki en büyük ve en dar P-dalgaları arasındaki fark bulunarak hesaplandı. Kontrol grubu henüz ilaç tedavisine başlanmamış hastalardan oluşturuldu. Tedavi öncesi ve sonrası ortalama PWD değerleri karşılaştırıldı.

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ÖZ

Bulgular: Ortalama yaş 53,6±8 bulundu. Referans ve kontrol EKG'sinde PWD değerleri hesaplandı ve karşılaştırıldı. Tamsulosin kullanımından önce ortalama PWD 55 ms (30-75) iken tamsulosin kullanımından 3 hafta sonra ortalama PWD 60 ms (45-70) olarak ölçüldü.

Sonuç: Tamsulosin kullanan hastalarda EKG'de PWD artışı istatistiksel olarak anlamlı bulundu. PWD artışı supraventriküler taşikardi riskinin arttığını gösteren bir bulgu olduğundan, bu grup hastalarda tamsulosin kullanırken klinisyenin daha dikkatli olması gerektiğini düşünmekteyiz.

Anahtar Kelimeler: Benign prostat hyperplasia, aritmi, alfa-bloker

INTRODUCTION

The use of alpha-adrenergic receptor blockers has opened a new era since the 1980s, particularly in the symptomatic treatment of patients who do not require surgery due to benign prostate hypertrophy (BPH). Initially developed to treat hypertension, the antihypertensive efficacy of these molecules is not very potent, the effects are short-acting, and the development of tolerance to the effect over time have made these drugs more or less adjuvant medication for treating hypertension (1). Lately noticed that they showed their primary effects on the urinary system. Over the years, molecules with more selective affinity for alpha-receptor subgroups and longer half-lives have been developed (2,3).

Alpha-adrenergic receptors are found in the heart, at the adrenergic nerve endings, and on the cell surface of myocytes. Roughly, clinical observations have shown that alpha receptor blockers neither cause cardiac arrhythmias, or significant changes inotropic. Studies on QT dispersion in electrocardiography (ECG) are available in the literature (4).

P-wave distribution (PWD) is a noninvasive indicator of atrial remodeling and an early predictor of atrial fibrillation (AF). PWD represents prolonged interatrial transmission and an insufficiently coordinated transmission system. In the ECG, the PWD is the value obtained by subtracting the duration of the shortest P-wave from the longest P-wave duration measured by evaluating the entire ECG in ms. The P-wave indicates the depolarization of the atria. The fact that the duration of P-waves is heterogeneous means that PWD increases. This is a sign that the current sinus rhythm is replaced by AF and less frequently atrial flutter (4,5).

We have not found any study in the literature whether PWD was altered by the use of alpha-adrenergic receptor blocking drugs. Therefore, we investigated the existence of this relationship in appropriate patients who will use alpha-blockers for symptoms of prostate hypertrophy and the lower urinary tract system.

METHODS

Between May 2017 and June 2017, 835 patients who applied to our clinic due to lower urinary tract symptoms (LUTS) were evaluated.

Patients have cardiovascular, endocrine system disease, and drug addiction were excluded from the study. The current study protocol was reviewed and approved by the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Institutional Review Board (decision no: 823, date: 22.08.2017). Informed consent was obtained from all the subjects upon enrollment.

Alpha-adrenergic blocker (tamsulosin) was started in 55 patients who met the study criteria. Each patient's pre-treatment electrolyte (which may cause ECG changes such as K, Ca, Mg, P) checked. Five patients who use their drugs intermittently due to the alpha blockers side effects were removed from the study even though they came to the control. Three patients were excluded because of gastrointestinal symptoms. Ten patients who did not come to the control were also excluded from the study. After 3 weeks of alpha-adrenergic blocker use, ECGs of 37 patients were recorded. PWD was compared in reference and control ECGs of all patients in the study. A control group was formed from patients who did not use the medication.

PWD was calculated manually by finding the difference between the largest and narrowest P-waves on the ECG. PWD measurements were compared before and after treatment. ECGs performed with ECG-9020K NIHON KOHDEN brand machine.

Statistical Analysis

Sample size calculated with G*Power Version 3.1.6. SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics are determined as number and percentage for categorical variables, mean, standard deviation, minimum, maximum, and median for numerical variables. If differences in the variables provided the normal distribution condition, the two dependent group comparisons were analyzed by the Paired t-test. When the normal distribution condition not provided, then the Wilcoxon signed-rank test was used. The statistical significance level of alpha was accepted as $p<0.05$.

RESULTS

Mean PWD before the administration of tamsulosin was 55 ms (30-75), while PWD was 60 ms (45-70) when tamsulosin

was used after 3 weeks (Figure 1, 2). The p-value was calculated as <0.001 (Table 1). Therefore, the p-value was considered statistically significant. The mean age is 53.6±8. The distribution of P-wave dispersions are shown in Figure 1. Moreover, we measured the P-wave dispersions and shown in Figure 2.

DISCUSSION

The use of alpha-blockers for LUTS and BPH is a treatment model that has been in used for many years in urology practice. In the choice of medication, the severity of symptoms, age, sexual activity of the patients should be questioned, as well as the patient's comorbidities, medications, and performance status (6,7).

The need to stop treatment due to orthostatic hypotension due to the use of alpha-blockers and to switch to more selective alpha-blockers has always led to the development of more selective drugs. Meanwhile, retrograde ejaculation, more frequently questioned in the first years, has become less questionable due to the increase in selectivity and the decrease in hypotensive side effects and increased efficacy (3,8,9).

It is hard to find patients who do not use any medication at this age. For this reason, investigating pure drug-related side effects is challenging. In particular, the side effects of urological drugs have begun to be questioned more and more recently, as in the FORTA study, due to changes in our patients' age, additional morbidities, and drug diversity (10).

Cardiac and especially pro arrhythmogenic side effects of alpha blockers have been studied in several studies based on the QT interval in the ECG. In a study by Herbert Lepor (11), it was determined that alfuzosin prolonged the QT interval statistically significant.

Recently, patients with no comorbidities and normal coronary angiography, who subsequently underwent embolism, acute coronary syndrome, and AF, were studied retrospectively (10). There are lots of studies that suggest P-wave variability exists in these patients and that PWD detected in these patients are pro important arrhythmogenic markers. Dilaveris et al. (5) found that PWD significantly prolonged idiopathic paroxysmal AF.

In our study, the effect-side effect profile of alpha-blockers are planned to investigate. Especially the proarrhythmic effects of these drugs. For this purpose, P-wave morphology and P-wave dispersion, which are accepted as decisive criteria, especially in detecting the tendency of AF, have been used in the literature today.

PWD is a simple ECG finding used to evaluate the spread of non-homogeneous sinus impulses in the atrium and inter-atrium communication (12). Prolonged PWD periods may be associated with stabilized angina pectoris and acute coronary syndrome, as well as in patients undergoing coronary artery bypass surgery. Studies conducted by Cheema et al. (4) and Tükek et al. (13) have reported that P-wave and PWD durations can be affected by autonomic control and increased sympathetic activity.

The primary outcome of our study is that the duration of PWD and the duration of the maximum P-wave measured

Table 1. Median P-wave dispersions

	Before the treatment	After the treatment	p-value
Median P dispersion (min-max)	55 (30-75)	60 (45-70)	<0.001

Serie 1: P-wave dispersion measured before tamsulosin usage
Serie 2: P-wave dispersion measured after tamsulosin usage
min-max: Minimum-maximum

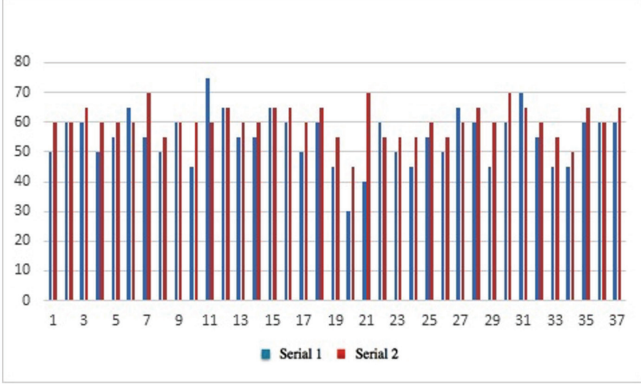

Figure 1. Distribution of P-wave dispersions
Serie 1: Without using tamsulosin
Serie 2: Using tamsulosin

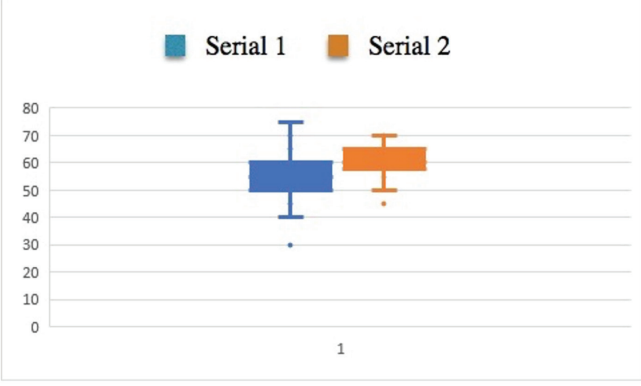

Figure 2. Measured P-wave dispersions
Serie 1: P-wave dispersion measured before tamsulosin
Serie 2: P-wave dispersion measured after tamsulosin

in the ECG of the patients who use of alpha-blockers due to BPH and LUTS are statistically significantly longer than in patients without drug use.

Additionally, patients with BPH without comorbidities were included in the study. Tamsulosin, a selective alpha blocker, was preferred. In polyclinics, 80% of patients were admitted with additional disease and multiple drug use. Considering the high use of non-selective alpha blockers in our country, the results of our study become more valuable.

CONCLUSION

In our study, we found that P-wave dispersion was prolonged in patients using tamsulosin due to benign prostate hyperplasia and lower urinary system symptoms. An increase in PWD is a finding that indicates an increased risk of supraventricular tachycardia. We should be more careful when using tamsulosin in these patients-

ETHICS

Ethics Committee Approval: The current study protocol was reviewed and approved by the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Institutional Review Board (decision no: 823, date: 22.08.2017).

Informed Consent: Informed consent was obtained from all the subjects upon enrollment.

Authorship Contributions

Surgical and Medical Practices: C.K., C.Y., Concept: C.K., S.L.K., Design: S.L.K., E.A., Data Collection or Processing: P.J., A.T.A., Analysis or Interpretation: C.Y., A.T.A., Literature Search: P.J., E.A., Writing: C.K., A.T.A., E.A.

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Research

Feasibility of Diffusion-weighted Magnetic Resonance Imaging for Differentiating Idiopathic Granulomatous Mastitis From Malignant Breast Lesions

İdiyopatik Granülomatöz Mastitin Malign Meme Lezyonlarından Ayırılmasında Difüzyon Ağırlıklı Manyetik Rezonans Görüntülemenin Uygulanabilirliği

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ABSTRACT

Objective: Idiopathic granulomatous mastitis (IGM) is an inflammatory breast disease that is often challenging to differentiate from malignancy. This study investigated the role of diffusion-weighted (DW) magnetic resonance imaging in differentiating IGM from malignant breast lesions.

Methods: This retrospective study included 82 female patients with IGM [with a mean age of 33.48 years, minimum (min): 22 - maximum (max): 58 years] and 85 female patients with breast cancer (with a mean age of 48.14 years, min: 31 - max: 79 years). The diagnoses of all patients were confirmed by biopsy, including 114 IGM lesions and 115 malignant lesions in the analysis. DW sequences were acquired with b-values of 0 and 1000 mm^2/sec on a 1.5 T device. The apparent diffusion coefficient (ADC) values of the lesions were measured manually by placing multiple regions of interest of 50-100 mm^2 in the target lesions and contralateral normal parenchyma.

Results: The ADC values of both IGM ($1.119\pm0.454\times10^{-3}$ mm^2/s) and malignant lesions ($1066\pm0.610\times10^{-3}$ mm^2/s) were lower than those of normal parenchyma. The ADC values of the mastitis group were significantly higher than the ADC values of the carcinoma group (p=0.00). The inter-observer (r=0.627) and intra-observer (r=0.775) agreement of ADC measurements were strong.

Conclusion: DW imaging is a useful noninvasive technique to differentiate between IGM and breast carcinoma.

Keywords: Granulomatous mastitis, magnetic resonance imaging, diffusion-weighted MRI, breast carcinoma

ÖZ

Amaç: İdiyopatik granülomatöz mastit (IGM), maligniteden ayırt edilmesi zor olan enflamatuvar bir meme hastalığıdır. Amacımız, difüzyon ağırlıklı (DAG) manyetik rezonans görüntülemenin IGM'yi malign meme lezyonlarından ayırt etmedeki rolünü araştırmaktır.

Gereç ve Yöntem: Bu retrospektif çalışmaya IGM'li 82 kadın hasta [ortalama yaş 33,48 yıl, minimum (min): 22 - maksimum (maks): 58 yıl] ve meme kanserli 85 kadın hasta (ortalama yaş 48,14 yıl, min: 31 - maks: 79 yıl) dahil edilmiştir. Tüm hastaların tanıları biyopsi ile kanıtlanmış olup, toplam 114 IGM lezyonu ve 115 malign lezyon çalışmaya dahil edilmiştir. 1,5 T'de 0 ve 1000 mm^2/sn b-değerlerinde DAG sekansları elde edildi. Lezyonların görünen difüzyon katsayısı (ADC) değerleri, hedef lezyonların ve kontralateral normal parankim içine 50-100 mm^2'lik bir alana sahip multipl ilgi alanları (*regions of interest*) yerleştirilerek manuel ölçüldü.

Bulgular: Hem IGM ($1,119\pm0,454\ x10^{-3}\ mm^2$/s) hem de malign lezyonların ($1066\pm0,610\ x10^{-3}\ mm^2$/s) ADC değerleri normal parankimden daha düşüktü. Mastitis grubunun ADC'leri, karsinom grubunun ADC'lerinden anlamlı derecede yüksekti (p=0,00). ADC ölçümlerinde gözlemciler arası (r=0,627) ve gözlemci içi (r=0,775) güçlü bir uyum vardı.

Sonuç: DAG, ve meme karsinomunu ayırt etmede yararlı, invaziv olmayan bir yöntemdir.

Anahtar Kelimeler: Granülomatöz mastit, manyetik rezonans görüntüleme, difüzyon ağırlıklı MR görüntüleme, meme kanseri

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INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a benign, recurrent, and prolonged inflammatory disease of the breast. It usually affects women of childbearing age with a history of lactation. Although it is reported to be a rare disease, its prevalence is uncertain. It has been reported to be more common in Hispanic, Asian, and Middle Eastern people, but can be seen in individuals of all races. The most common clinical manifestation of IGM is a unilateral painful, palpable breast mass (1-4). There may also be coexisting palpable axillary lymph nodes, which can be confused with axillary metastatic breast cancer (2-5). The imaging findings are non-specific and vary depending on the stage of the disease and the extent of inflammation (2,5-11). The differential diagnosis of IGM included malignancy and other inflammatory breast diseases. A definitive diagnosis of IGM requires the exclusion of these diseases and histopathological confirmation (2,5,6). Histopathological examination of IGM reveals non-caseating granulomatous inflammation accompanied by lobulocentric acute and chronic inflammatory cells with preserved major ducts and surrounding adipose tissue. Necrosis and fibrosis are less noticeable (12-15).

Diffusion-weighted (DW) magnetic resonance (MR) imaging is a functional modality that allows for the quantitative measurement of the mobility of water molecules *in vivo* to provide numerical data with apparentclear diffusion coefficient (ADC) values without using contrast material. It analyzes the microscopic structure of tissues such as cellularity, membrane integrity, viscosity, organelles, and macromolecules (16). Some studies have found ADC values to be useful for the differentiation between malignant and benign lesions, while others have reported that they are useless due to the significant overlap of ADCs (17).

This study investigated the feasibility of mean ADC values for differentiating IGM from malignant breast lesions.

METHODS

The study was designed as a retrospective study and approved by our University of Health Sciences Türkiye Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee Institutional review board (approval decision no: 514/190/4, date: 25.11.2020). The requirement for obtaining informed consent from the patients was waived.

Study Population

Data of patients who were histopathologically diagnosed with IGM and breast cancer between January 2016 and October 2020 were evaluated. When diagnosing IGM, microbiological tests (gram staining, periodic acid-Schiff and acid-fast staining, mycobacterial cultures, fungal analysis with methenamine silver staining) were carried out to differentiate it from other bacterial and fungal mastitis infections. Moreover, purified protein derivative skin (PPD) test and blood tests were performed for differentiate between tuberculosis mastitis and IGM.

The study included patients with pre-treatment MR examinations. Patients without an MR examination and with postoperative or post-neoadjuvant chemotherapy MR examination, male patients, and patients with images unsuitable for ADC measurement secondary to artifacts were excluded from the study. Lesions smaller than 1 cm were excluded from the study to avoid the partial volume effect. The lesions that were noted on MR examination of patients based on the study inclusion criteria were included in the analysis. In cases of bilateral breast cancer and post-mastectomy recurrent breast cancer in the contralateral breast, ADC measurement was not performed from the contralateral breast parenchyma.

MR Imaging (MRI) Technique

MR were examined on a 1.5 T device (Ingenia Philips Healthcare, Best, the Netherlands). Non-fat-saturated turbo-spin-echo T1 ([field of view (FOV): 302x302 mm, Matrixmatrix: 199x203, flip angle (FA): 90 deg, repetition time (TR): 547 ms, echo time (TE): 8 ms, slice thickness: 3.00 mm, Slice slice gap: 3.30)], spin-echo short tau inversion recovery (FOV: 341x341 mm, Matrixmatrix: 263x223, FA: 90 deg, TR: 4040 ms, TE: 65/175.000 ms, slice thickness: 3.00 mm, slice gap: 3.30), three -dimensional fat-saturated ultrafast spoiled gradient-echo dynamic (FOV: 342x342 mm, Matrixmatrix: 342x340, FA: 10 deg, TR: 5 ms, TE: 3 ms, slice thickness: 2 mm, Sslice gap: 1 mm), and DW (FOV: 364x364, Matrix matrix 151x146, FA: 90, TR: 9400, TE: 71, slice thickness: 3, Slice slice gap: 3) sequences were retrieved. All sequences were acquired in the transverse plane. Dynamic sequences consisted of 5 series, one of which was pre-contrast (90, 142, 194, 246, 298 seconds after injection).

DW sequences were obtained with b-values of 0 and 1,000 mm^2/sec on both devices. All were examined in the prone position using a dedicated 16-channel phased-array breast coil in the prone position. A single dose of 0.1 mmol/kg body weight gadolinium chelate was administered to patients with the aid of an automated injector.

Image Analysis

MR images and ADC measurements were independently assessed by two radiologists (G.R, M.A.), with 6 and 9 years of experience in breast imaging. All MR images

were reviewed in the picture archiving and communication system on the EIZO GS520 workstation. Pre-treatment MR examinations of patients were assessed in both groups. The first group included patients with IGM, whereas the second group included patients with breast cancer. Enhancing masses and non-mass enhancements (NME) were evaluated in patients with IGM. Maximal lesion diameter and average ADC values for IGM and malignant lesions were noted. The maximal lesion diameter was measured in the first post-contrast dynamic series. ADC measurements were carried out in accordance with the recommendations of the European Society of Breast Radiology (18). ADC was measured manually by placing multiple regions of interest (ROIs) with areas ranging from 50-100 mm^2 into the lesion. Multiple ROIs were used as much as they could fit into the lesion. (Figures 1, 2). Other ROIs were obtained by duplicating the first ROI in each lesion. The average of these measurement results was taken for each lesion. In the measurements, the largest visible cross-section of the solid component of the lesions was selected. Dynamic contrast enhanced DCE-MR images were used as references. Measurements were made by placing ROIs in the enhanced parts of the lesions, taking care not to exceed the borders of the lesions. Necrotic and hemorrhagic components were avoided during the measurement. ADC values were also measured from the contralateral normal breast parenchyma in each patient. No measurement was performed from the contralateral parenchyma in patients with previous mastectomy or bilateral breast involvement. The readers were blind to each other's other's results and the patient's patient's diagnosis. After performing ADC measurements for all patients, the readers repeated ADC measurements for the same patients.

Statistical Analysis

The study data were analyzed using the Statistical Package for Social Sciences (SPSS) version 17.0 software. Descriptive statistics are presented as mean, minimum (min), maximum (max), standard deviation, and percentage . The one-sample Kolmogorov-Smirnov test was used to check whether numerical data follow a normal distribution or not. The Mann-Whitney U test was used to compare data that did not show normal distribution (ADCs of lesions and normal parenchyma) between the mastitis and carcinoma groups. Spearman's Spearman's rho test was used to evaluate inter- and intra-observer concordance, which included non-normally distributed parametric data. A p-value <0.05 was considered statistically significant.

RESULTS

Of the 87 patients with IGM, 4 without MR examination and 1 with no ADC measurement secondary to artifacts were excluded from the study. Of the 951 patients with breast cancer, 2 male patients, 828 without pre-treatment MR examination, 28 with post-neoadjuvant chemotherapy MR examination, and 8 with DW images unsuitable for ADC measurement secondary to artifacts were excluded from the study. ADC was not measured from the contralateral normal breast parenchyma in 1 patient with bilateral breast

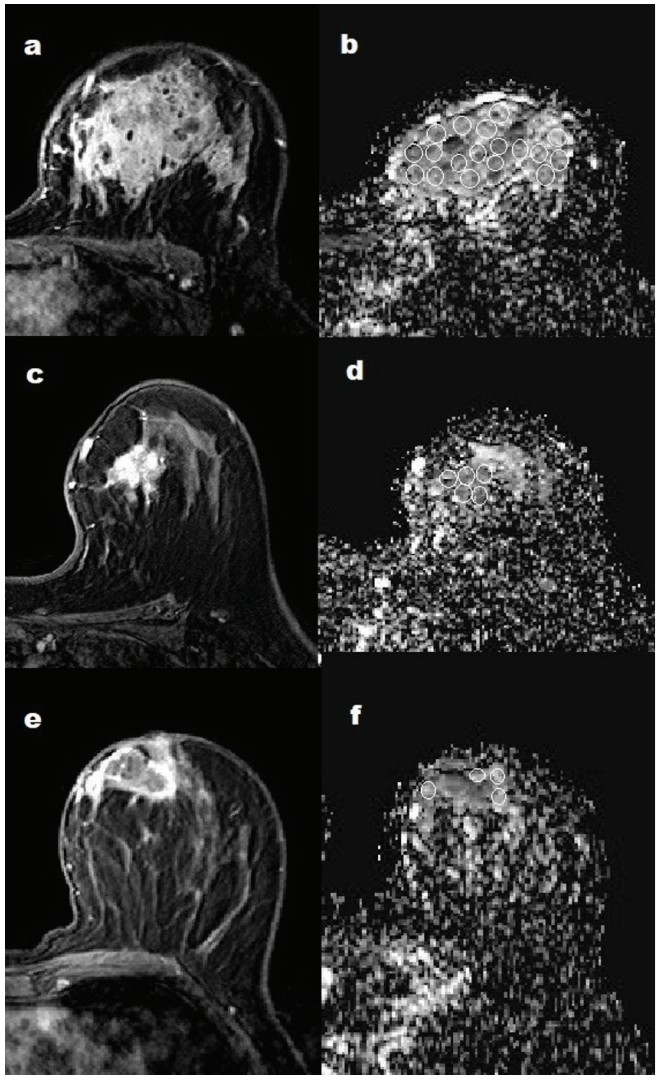

Figure 1. (a, b) The DCE-MR image of a 20-year-old patient with a diagnosis of IGM shows a large area of NME and microabscesses in the left breast. A low signal intensity was measured in this area on the ADC map. (c, d) A 36-year-old patient with a diagnosis of IGM has an enhancing mass lesion in the left breast on DCE-MR image. ADC values were measured from the mass on the ADC map. (e, f) A 42-year-old patient with IGM had a central non-enhancing abscess in the left breast. A low signal intensity is noted in the central part on the ADC map, while a higher signal intensity is visualized on the enhancing wall. ADC measurement was taken from the wall

ADC: Apparent diffusion coefficient, IGM: Idiopathic granulomatous mastitis, DCE-MR: Dynamic contrast-enhanced-magnetic resonance

cancer and in 3 patients who had previously undergone mastectomy.

The study included 82 female patients with IGM (with a mean age of 33.48 years, min: 22 - max: 58 years) and 85 female patients with breast cancer (with a mean age of 48.14 years, min: 31 - max: 79 years). A total of 114 IGM lesions and 115 malignant lesions were assessed.

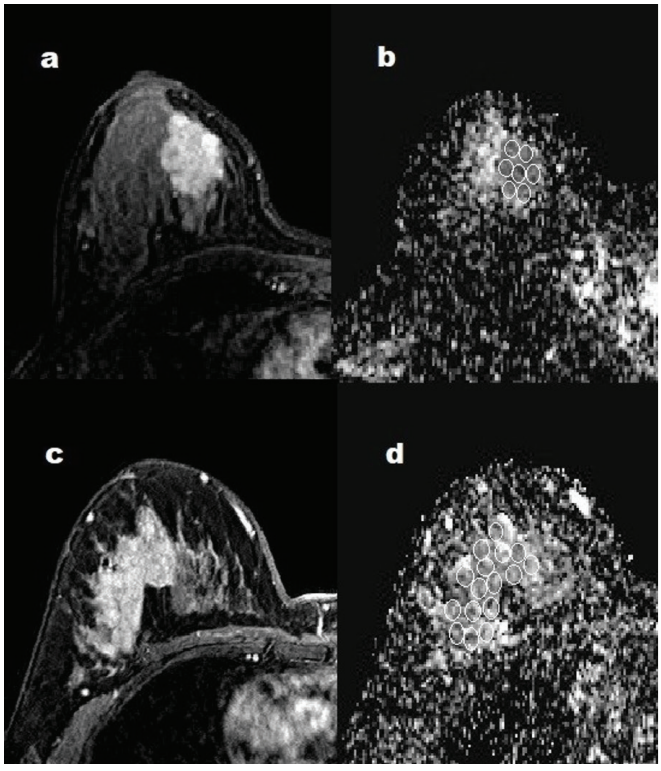

Figure 2. (a, b) The DCE-MR image of a 32-year-old patient with a diagnosis of invasive ductal carcinoma shows an enhancing mass in the right breast. ADC measurement was made from its counterpart on the ADC map. (c, d) The DCE-MR image of a 37-year-old patient; the biopsy result of the NME in the right breast is DCIS. Multiple ROIs were measured from this lesion, which displayed a low signal intensity on the ADC map

ADC: Apparent diffusion coefficient, DCIS: Ductal carcinoma in situ, ROIs: Regions of interest, NME: Non-mass enhancements

According to the histological types, 100 (86.96%) of malignant lesions were NST (no special type), 7 (6.08%) were ductal carcinoma in situ, 6 (5.22%) were lobular carcinomas, and 2 (1.74%) were mucinous carcinoma.

ADC values of both IGM and malignant lesions were lower than those of the normal parenchyma. The ADC values of the mastitis group were significantly higher than the ADC values of the carcinoma group (p<0.0.001) (Table 1). The comparison of the ADC values of abscesses, masses, and NME lesions in the IGM group showed a statistically significant difference between the ADCs of abscesses and the other two lesion groups (p=0.001). However, there was no difference between the ADCs of masses and NME lesions (Table 2). There was no significant difference between the ADCs of mass and NME lesions in the carcinoma group (p=0.8) (Table 3).

There was a strong positive correlation between the ADC measurements made by the first and second observers (r=0.627). A strong positive correlation was found between the intra-observer agreement of ADC measurements (r=0.775).

DISCUSSION

IGM presents with various nonspecific imaging findings and may mimic malignancy and other inflammatory lesions. The most common mammographic findings of IGM include focal

Table 3. ADC values and dimensions of carcinoma lesions by mass and NME subgroups

Carcinoma (n=115)	Mass (n=93)	NME (n=22)	p-value
Lesion size ± SD (mm)	28.49±13.12	37.19±18.06	0.053
Mean ADC (x10^{-3}mm^2/s)	1.072±0.618	1.036±0.589	0.800

ADC: Apparent diffusion coefficient, SD: Standard deviation, NME: Non-mass enhancements

Table 1. Size and ADC values of IGM and carcinoma lesions

Lesion groups	IGM (n=114)	Carcinoma (n=115)	p-value
Lesion size ± SD (mm)	40.15±20.59	30.13±14.46	<0.001
ADC mean ± SD (x10^{-3}mm^2/s)	1.119±0.454	1.066±0.610	<0.001

SD: Standard deviation, ADC: Apparent diffusion coefficient, IGM: Idiopathic granulomatous mastitis

Table 2. Size and ADC values by subgroups of IGM lesions

IGM lesions (n=114)	Abscess (n=54)	NME (n=39)	Mass (n=21)	p-value
Lesion size ± SD (mm)	34.35±22.84	44.74±19.37	46.00±12.05	<0.001
Mean ADC (x10^{-3}mm^2/s)	1.198±0.471	1.066±0.459	1.015±0.381	0.001

SD: Standard deviation, ADC: Apparent diffusion coefficient, IGM: Idiopathic granulomatous mastitis, NME: Non-mass enhancements

or global asymmetry and irregularly shaped mass, with non-specific findings. The ultrasound findings of IGM are irregular hypoechoic mass with tubular extension, heterogeneous hypoechoic mass (or confluent masses) with indistinct, lobulated, or angular margins, and abscess (1,2). Lesions and contrast enhancement patterns, which can also be seen in malignant lesions, have been reported on MRI of IGM. The most common lesions include heterogeneous or ring-enhancing mass lesions and NME. Segmental and regional enhancement patterns have most frequently been reported for NME lesions. Clumped-ring enhancement, which is highly suggestive of malignancy, can also be seen (1,2,5-7).

DW imaging is central to the detection of breast lesions, the differentiation between malignant and benign lesions, the characterization of malignancy, and the evaluation of tumor spread. ADC values of malignant breast lesions have been reported to be lower than those of benign breast lesions (17,18). It has been suggested that low ADC values of malignant tumors are due to increased cell density, larger nuclei, larger macromolecular protein content, and decreased extracellular space (19). Matsubayashi et al. (20) suggested that DW imaging of breast carcinomas was affected not only by cell density but also by structural variations in the stroma (20). Previous studies have found that the ADC values of IGM lesions are lower than those of the normal parenchyma (6,21,22). In line with these studies, the results of this study demonstrated lower ADC values for IGM lesions compared with normal parenchyma. This may be due to the narrowed extracellular space by the dense accumulation of inflammatory cells in the areas occupied by IGM and the viscous inflammation of abscess formations. Additionally, the absence of necrosis in IGM may be the cause of low ADC values.

Kang et al. (23) found that DW imaging was successful in rim-enhancing inflammatory and malignant lesions. In this study, inflammatory breast lesions demonstrated typical central hyperintensity, whereas breast cancers demonstrated peripheral hyperintensity (23). Previous studies have investigated the efficacy of ADC values for the differentiation between mastitis and breast carcinoma (21,24-28). However, the results of these studies are inconsistent, which may be due to differences in patient populations and variations in MR techniques or measurement methods.

According to the results of our study, DWI is useful for distinguishing between IGM and breast carcinoma and may increase the specificity of MR for the diagnosis. A study by Yilmaz et al. (22) comparing ADCs of IGM and malignant breast lesions reported that ADC values failed to differentiate IGM from malignant lesions (22). The reason for different results of our study may be the ADC measurement method. In this study, ROIs were placed only in the viable component of the lesions, excluding necrotic parts. Additionally, the wall of abscess formation containing living tissue was measured, rather than the central pus component. The b-values used in this study may have also affected the results.

In our study, lesion type and ADC values were not correlated in both IGM and malignant lesions, except for abscesses. There is an overlap in ADC values for the differentiation between mass and NME in IGM and malignancy. This result may be attributed to the heterogeneous internal structure of the breast lesions. In this study, DW images were acquired with high b-values (0 and 1000), which were within the recommended range for breast examinations. A high b-value was chosen because of the decreased T2 and perfusion effect and the increased diffusion effect with high b-values.

A limitation of this study is the non-inclusion of b-values. However, a study by Pereira et al. found no benefit of higher b-values in differentiating between breast lesions (24). The retrospective nature of the study is another limitation. The study is limited by not considering the menstrual cycles of the participants, which affects the background contrast when performing MRI.

CONCLUSION

In conclusion, this study compared the ADC values of IGM and malignant breast lesions. The results of the study demonstrated the feasibility of ADC values for distinguishing IGM from malignant lesions. DW-MRI imaging, a non-invasive technique that does not require the use of contrast media, can help differentiate between IGM and breast carcinomas. The advantage of this technique is that DW imaging does not require intravenous contrast media and does not emit radiation.

ETHICS

Ethics Committee Approval: The study was designed as a retrospective study and approved by University of Health Sciences Türkiye Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (decision no: 514/190/4, date: 25.11.2020).

Informed Consent: The requirement for obtaining informed consent from the patients was waived.

Authorship Contributions

Surgical and Medical Practices: Ş.K., K.Ç., Concept: G.R., M.A., Design: G.R., M.A., N.V., Data Collection or Processing:

G.R., M.A., Ş.K., K.Ç., Analysis or Interpretation: G.R., M.A., N.V., Literature Search: G.R., Writing: G.R.

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

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Research

The Experience of Women Infected by the COVID-19 During Pregnancy: A Qualitative Study

Türkiye'de Gebelik Döneminde COVİD-19 ile Enfekte Olan Kadınların Deneyimleri: Nitel Bir Araştırma

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ABSTRACT

Objective: To gain deeper understanding of experiences of pregnant women infected with coronavirus disease-2019 (COVID-19) during the pandemic.

Methods: This study, which was planned as a descriptive qualitative study, was performed out with 15 pregnant women infected with COVID-19. The data were collected between January 5th and March 15th, 2021 using a semi-structured interview form and in-depth interview method. Content analysis, one of the qualitative research method, was used to evaluate the data. The research was planned based on the Qualitative Research Reporting Consolidated Criteria checklist, which is a guide for qualitative research.

Results: Four main themes were found in experiences of pregnant women infected with COVID-19: (1) "psychosocial health"; (2) "change in daily routines on quarantine days", (3) "coping" and (4) "perinatal period changes". Pregnant women experienced both psychological and physical difficulties. They used the expression "closed box" to describe the anxiety and anxious state experienced due to the uncertainty of the perinatal outcomes brought about by COVID-19 during pregnancy.

Conclusion: Understanding the experiences of pregnant women infected with COVID-19 is the first step in determining treatment and care management for nurses and healthcare professionals. During the pandemic period, pregnant women need to reach prenatal care services on time, to support them physically and psychosocially, to provide information with e-health services, and to provide remote follow-up support to cope with the process.

Keywords: COVID-19, pregnancy, qualitative research

ÖZ

Amaç: Bu çalışma Türkiye'de pandemi sürecinde koronavirüs hastalığı-2019 (COVİD-19) ile enfekte gebelerin deneyimlerini daha derinden belirlemek amacıyla planlanmıştır.

Gereç ve Yöntem: Tanımlayıcı niteliksel tipte planlanan bu çalışma, COVİD-19 ile Enfekte 15 gebe ile gerçekleştirilmiştir. Veriler 5 Ocak-15 Mart 2021 tarihleri arasında yarı yapılandırılmış görüşme formu ile derinlemesine görüşme yöntemi kullanılarak toplanmıştır. Verilerin değerlendirilmesinde niteliksel araştırma yöntemlerinden içerik analizi yapılmıştır. Araştırma nitel araştırmalar için rehber niteliğindeki Kalitatif Araştırma Raporlama Konsolide Kriterleri kontrol listesi temel alınarak planlanmıştır.

Bulgular: COVİD-19 ile enfekte gebe kadınların deneyimleri ile ilgili 4 ana tema belirlendi: (1) "psikososyal sağlık"; (2) "karantina günlerinde günlük rutinlerde değişiklik"; (3) "başa çıkma"; (4) "perinatal dönem değişiklikleri"dir. Gebeler hem psikolojik hem de fiziksel bazı zorluklar yaşamışlardır. Katılımcılar COVİD-19'un gebelik sırasında getirdiği perinatal sonuçların belirsizliği nedeniyle yaşanan kaygı ve endişeli durumu tanımlamak için "kapalı kutu" ifadesini kullanmışlardır.

Presented in: This study was presented as an oral presentation at the "2nd International 4th National Childbirth Education and Educators Congress" held on 27-30 October 2022.

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ÖZ

Sonuç: COVİD-19 ile enfekte olan gebelerin deneyimlerini anlamak, hemşireler ve sağlık profesyonelleri için tedavi ve bakım yönetimini belirlemede ilk adımdır. Pandemi döneminde gebelerin doğum öncesi bakım hizmetlerine zamanında ulaşması, fiziksel ve psikososyal anlamda desteklenmesi, e-sağlık hizmetleri ile bilgilendirme ve uzaktan takip desteğinin yürütülmesi süreçle başa çıkmaları açısından önemlidir.

Anahtar Kelimeler: COVİD-19, gebelik, nitel araştırma

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 2019 was a virus causing coronavirus disease (COVID-19) (1). COVID-19 was a new coronavirus family potentially affecting all segments of society, and whose clinical path was not completely developed for vulnerable populations, including pregnant women (2,3).

At the time of data collection, there was no safe and effective treatment for COVID-19 during pregnancy (4). In addition, none of the vaccines were subjected to specific clinical trials in pregnant women (1,5).

In the general population, the pandemic resulted in a rise in anxiety and other mental health issues (5,6). Furthermore, restrictions on movement limited interpersonal contact (6). Fear, stress, and anxiety were triggered by factors such as the rapid spread of the disease, a rise in the number of outbreaks, a lack of knowledge about the disease, uncertainties due to misunderstandings about the disease, and fear of the unknown (7). There was evidence that COVID-19 added to the anxiety of women already affected by the uncertainties that surround pregnancy (5,8). Concerns experienced by pregnant women were thought to be due to multiple causes, including COVID-19 itself, reduced support from family and friends due to social isolation, the potential for decreased income, and significant changes in perinatal care (5). Additionally, participation in prenatal appointments decreased due to COVID-19 restrictions and their increased anxiety (7,9) due to the risk to both themselves and their fetus (7). Meta-analyzes and systematic reviews have concluded that there were increases in the rates of perinatal mental health disorders, including anxiety and depression during the pandemic (5). A recent study with pregnant women in Italy found that more than half of the participants were seriously psychologically impacted by COVID-19 (2). It is known that anxiety and stress during pregnancy are associated with adverse outcomes such as preeclampsia, depression, nausea and vomiting, low birth weight (7,10), preterm birth, and low APGAR score (7). It was therefore predicted that the psychological consequences of the epidemic could have a major impact on pregnant women with COVID-19 (9).

Little was known about how pregnant women cope with the current coronavirus outbreak and its consequences (8). At this time, pregnant women and their families are particularly in need for the support of healthcare personnel, especially nurses, and it is important to determine how such support can be delivered (7). Qualitative research provides an understanding of the thoughts, views, beliefs, and attitudes of a homogeneous population group on a particular subject (2). Qualitative research conducted during the COVID-19 pandemic allows access to and interpretation of epidemiological data on experiences and perceptions of the disease and the epidemic (11). Thus, it is essential to conduct such studies across different population groups at different time periods (2). The aim of this study was to determine the experiences of pregnant women infected with COVID-19 during the pandemic, and to create a data source for nurses and healthcare professionals to refer to in the event of possible similar situations.

METHODS

Design and Sample

In this qualitative study, a phenomenological approach was taken to reveal the experiences of pregnant women with COVID-19, using in-depth interviews.

The sample consists of pregnant women over the age of 18 diagnosed with COVID-19 during pregnancy who subsequently recovered, and who can speak Turkish Being diagnosed with a major psychiatric disease was determined as the exclusion criteria.

Sampling Strategy

To avoid the need for extended face-to-face communication with the pregnant women during the period of social isolation, the interviews were conducted via cell phones. To find interviewees, the snowball sampling method was used to identify pregnant women who recovered after being diagnosed with COVID-19 (12). The first interview was conducted with a contact among the researchers' colleagues. This led to further contacts, and a working group was formed by asking each interviewee "Who else would you recommend we meet with, who was diagnosed with COVID-19 during pregnancy?" "Data saturation" is a

critical criterion in assessing the sample size in qualitative studies (13). Data collection continued until the concepts and processes (saturation point) that addressing the research questions began to repeat. Data saturation (n=15) triggered the end of qualitative data collection.

Setting

In Turkey, at the time of the data collection, those who were positive for COVID-19 or who were in close contact with these individuals were monitored in quarantine for 14 days, after which quarantine was lifted. COVID-19 vaccination started on January 14, 2021, with the approval of the Ministry of Health of the Republic of Türkiye. However, at the time of the study, no pregnant women had yet been vaccinated, including all participants. Twelve of the participants were asymptomatic and 3 of them were mildly symptomatic (fever or cough). All of the pregnant women were followed at home during the illness. Participants were interviewed during pregnancy only after they had recovered from the COVID-19 infection. Pregnancy outcomes were not monitored.

Data Collection Method

The data of the study were collected in semi-structured interviews held between January 5 and March 15, 2021. Three experts were involved in constructing the interview questions.

There are two aspects of the data collection form. To initiate the interviews, and as a transition to the main subject, the introduction section includes questions about socio-demographic and obstetric characteristics, such as age, education level, number of pregnancies, and use of assisted reproductive techniques. The second segment consists of ten open-ended, semi-structured interview questions (Table 1). The clarity of the interview form was tested with a pregnant woman who was diagnosed with and recovered from COVID-19, and had identical characteristics to the sample community. In each interview, the researchers sought and obtained the name and contact details of another potential participant. All interviewees were contacted by researchers well ahead of the interview time, after they had been personally informed by the person who suggested them. The participant was then contacted by researchers, informed that the telephone conversation would be recorded, and the meeting was scheduled a time convenient for the participant. It was recommended that the participant was in a quiet place for the interview, so that she could talk freely without distraction.

The interviews were conducted as teleconferences with the pregnant woman and two researchers present. A researcher interviewed the pregnant woman, while the other assisted in documenting the interview and noting the key points. All interviews lasted between 30-45 minutes. Participants were given the opportunity to make additional comments at the conclusion of the interview. The second author has experience of qualitative research in courses and lectures in her doctoral education, and in her doctoral thesis.

Data Analysis

The analysis of the data was carried out by all researchers based on the method proposed by Graneheim and Lundman (14). Following the interviews, the researchers listened to and transcribed the audio recordings. The participants were asked to check the accuracy of the deciphered text, and their feedback was collected.

First, the researchers reread the interviews many times to obtain a sense of the overall content of the text and to develop an analytical infrastructure relevant to the potential codes in the readings. Initial codes were decided, and drafts were made based on the inferences. The first level starting codes were collected under main themes and sub-themes. A more abstract grouping was achieved by rearranging the initial sub-themes by renaming, combining and removing irrelevant subthemes. The researchers then edited the data and interpreted the results before reaching a final consensus, which resulted in the development of 19 sub-themes, grouped

Table 1. Semi-structured open-ended interview questions

Questions about the experiences of pregnant women diagnosed with COVID-19
1. How has COVID-19 affected your life? Could you share with me?
2. When you found out your COVID-19 test was positive, how did you feel and what did you think? Could you share with us?
3. How did the quarantine process affect your follow-up and antenatal care after you were diagnosed with COVID-19? Could you share with us?
4. How were your relationships with family members after being diagnosed with COVID-19? Could you share with us?
5. How were your relationships with social environment after being diagnosed with COVID-19? Could you share with us?
6. What are your thoughts your own self, baby and on birth? Could you share with us?

COVID-19: Coronavirus disease-2019

into four main themes. The participants' key statements for descriptive analysis were cited, selected according to the themes, and study questions formed within the conceptual framework. An external auditor with expertise in qualitative analysis was consulted to confirm the appropriateness of the results and interpretation of the coding. To ensure the study's validity and reliability, the researchers employed the principles of transferability, consistency, verifiability, and credibility. In direct quotes, the labels "P1, P2, ... P15" were used to preserve the participants' privacy. The 32 guidelines of the COREQ checklist were used in reporting the qualitative research (15). Content analysis, one of the qualitative research methods, was used in the evaluation of the data, so statistical analysis didn't used.

Truthfulness

We used three criteria to ensure the rigor of the analysis and the trustworthiness of the results: reliability, verifiability, and transferability (16). The researchers determined the main themes and sub-themes that should be clustered with similar ideas to ensure reliability. All authors read the transcripts of the interview data. This analysis procedure continued until a consensus was reached among the authors. The authenticity of the data has been preserved to increase the reliability. To ensure accuracy, an expert experienced in qualitative research and familiar with the study was consulted on the relevance of the main theme and sub-themes. In providing transferability, the snowball sampling method was used to find the most appropriate sample. The participants were interviewed twice; in the first meeting, information was given about the content of the interview, and in the second, data were collected and participant confirmation was obtained. Participant confirmation was sought immediately after data collection; the researchers summarized the data collected and asked the participants to comment on its accuracy. Additionally, the this also gave participants had the opportunity to add further experiences. For transferability, data are presented by quoting directly from participant statements.

Ethical Considerations

Ethical permission was obtained from the İzmir University of Economics Ethics Committee for the study (approval no: B.30.2.İEÜSB.0.05.05-20-099, date: 21.12.2020), and the T.C. The ministry of Health's COVID-19 Scientific Research Assessment Commission granted the requisite approval.

Table 2. Socio-demographic characteristics of the participants

Participant number	Age	Education level	Profession	Occupational status	Week of infected by COVID-19	Interviewed week	Parity	Type of conception
P1	31	University	Nurse	Working	16th weeks	24th weeks	Multiparous	Spontaneous pregnancy
P2	28	University	Nurse	Working	18th weeks	24th weeks	Multiparous	Spontaneous pregnancy
P3	31	University	Nurse	Working	17th weeks	29th weeks	Primiparous	Spontaneous pregnancy
P4	32	University	Medical secretary	Working	15th weeks	22nd weeks	Multiparous	Spontaneous pregnancy
P5	31	High school	Radiology technician	Working	29th weeks	36th weeks	Multiparous	Spontaneous pregnancy
P6	37	University	Fashion designer	Working	33rd weeks	36th weeks	Primiparous	Spontaneous pregnancy
P7	32	University	Nurse	Working	4th weeks	24th weeks	Multiparous	Spontaneous pregnancy
P8	35	University	Academician	Working	26th weeks	31st weeks	Primiparous	In vitro fertilization
P9	32	University	Pre-school teacher	Working	12th weeks	18tth weeks	Multiparous	Spontaneous pregnancy
P10	27	University	Housewife	Not working	14th weeks	27th weeks	Multiparous	Spontaneous pregnancy
P11	28	University	Medical doctor	Working	11th weeks	22nd weeks	Primiparous	Spontaneous pregnancy
P12	33	University	Nurse	Working	23rd weeks	31st weeks	Multiparous	Spontaneous pregnancy
P13	31	University	Nurse	Working	23rd weeks	33rd weeks	Multiparous	Spontaneous pregnancy
P14	36	University	Manager	Working	3rd weeks	17th weeks	Multiparous	Spontaneous pregnancy
P15	30	University	Teacher	Working	23rd weeks	28th weeks	Primiparous	Spontaneous pregnancy

The participants were told about the study's aim, and that the interviews would be recorded. Since written consent could not be obtained, a text containing the required explanations about the study's aims was created on a Google Form, and a message with the connection link was sent to participants to obtain their consent. Furthermore, at the beginning of the interview, verbal consent was obtained. Copies of both the participants' interview transcripts and data were kept in a computer environment with a password known only to the researchers. This study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Information containing various sociodemographic characteristics of the participants are given in Table 2. The experiences of pregnant women infected with COVID-19 during the pandemic were discussed under four main themes: "psychosocial health, change in daily routines on quarantine days, coping and perinatal period changes", and a total of 20 subthemes (Table 3).

Table 3. Experiences of women infected by COVID-19: Main themes and subthemes

Main themes	Subthemes
Psychosocial health	Sadness and desperation
	Fear
	Worry and anxiety
	Anxiety
	Contagion source searches
Changes in daily routines on quarantine days	Short break time
	Sensitivity of cleaning and hygiene
	Difficulty in taking care of children
	Social distance
Coping methods	Social support
	Strengthening immunity
	Beliefs and pray
	Avoidance from social media news
	Thought of "I survived COVID"
Perinatal period changes	Failures of tests and examinations
	Postponement of tests and examinations
	Changes in hospital selection for delivery
	Fear of being alone at home
	Increases in health expenditures
	Worries about postpartum visits

COVID-19: Coronavirus disease-2019

Psychosocial Health

The effects of being COVID-19 positive during pregnancy on the psychosocial health of women were examined under four headings: sadness and desperation, fear, worry and anxiety, and search for contagion source.

Sadness and Desperation

More than half of the pregnant women stated that they could not believe that had caught COVID-19 and that they felt very helpless and sad, especially those who had the disease at the same time as their spouses. Some expressions are given below:

My world collapsed on my head, and I wanted to throw myself off the ground . . . (P6)

I was feeling desperation. I had nobody but my husband. We were both sick, and I wondered if it could get worse. (P15)

Fear

Almost all of the multiparous pregnant women stated that they were most afraid of transmitting the disease to their children on learning that they had COVID-19.

I have a three-and-a-half-year-old son, will it pass to him? Will my baby be affected during my pregnancy? (P10)

One of the pregnant women stated that her mother had a chronic illness and was afraid that she would die if infected with COVID-19;

I said, "If I infect my mother, my mother will definitely die…" I felt incredible remorse. I could not sleep. (P5)

Worry and Anxiety

Some pregnant women experience uncertainty about the future of their fetuses, children, and themselves due to COVID-19 infection, describing this situation as a "closed box", due to lack of clarity about the health of the fetus during pregnancy.

…We had all our antenatal tests, and had some extra tests, but I am still worried, I mean this is a blackbox… (P3)

Some pregnant women were worried about who would take care of their living child if something happened to them.

…What happens to my children if I die. (P5)

The majority of pregnant women were afraid of becoming reinfected with COVID-19 in a more severe form before giving birth.

Last week, I had a sore throat. I was done, I screamed, I lost myself worrying if I were corona again. (P6)

Some pregnant women stated that they were unable to prepare for the baby, due to the anxiety that "something would happen".

There was no study on the first trimester. I was very scared, in the first weeks, there may be intrauterine growth retardation. The pulse is the first thing I want to see on an ultrasound every time. . . I don't want to buy her any clothes or something right now, for example. . . (P11)

Contagion Source Searches

Some of the pregnant women reported that they followed all precautions as instructed, even going so far as to exaggerate them at times, but that this had not stopped infection. Especially participants who were healthcare professionals reported feeling powerless due to circumstances beyond their control (e.g., their spouse's employment, working in a crowded environment, etc.).

…I was really extremely careful about the measures. I was wearing a visor and an N95. I was conscious of my social distance and avoided doing anything unless wearing gloves, but the result was failure. (P3)

Some women also blamed their spouses for bringing the disease, despite taking every precaution.

… I did not meet people. I was working flexibly at home . . . I did not even meet my own parents . . . But it came from my husband. (P8)

A pregnant woman expressed her discomfort at being close to the children as she was a classroom teacher, but could not change this.

… I feed the children, change their clothes, perform all kinds of caring. I admit that we do not follow the rules of social distance. I have no chance to say, "Please don't hug me, let's keep our distance." (P9)

Changes in Daily Routines on Quarantine Days

The lives of pregnant women infected with COVID-19 have changed in a matter of days due to the disruption of daily routines. While some of the working pregnant interpreted it as a short break from work and rest time, some of them mentioned the difficulties of social isolation at home.

A Short Breaktime

Some of the pregnant women (n=2) considered the quarantine phase as a short break from the hectic pace of work.

Of course, does this disease can not be an advantage, but my husband and I both work really hard. It was good to spend 15 days together. (P9)

Sensitivity of Cleaning and Hygiene

Some pregnant women, especially those without a private space at home, stated that they had to pay extra attention to hygiene to prevent the disease from spreading to their family members.

I had a bath after everyone else was asleep. I disinfected the bathroom and sink after each use. I used cardboard cups and changed toothbrushes all the time. Households were not infected… (P14)

Difficulty in Taking Care of Children

During the quarantine period, some pregnant women stated that they felt extremely tired due to COVID-19 and that they could not spare time for their children.

It doesn't benefit you or your child much because you do not feel well or safe. It is inefficient and you cannot spare a lot of time. (P1)

Social Distance

Some of the pregnant women stated that they tried protecting their spouses, but because they could not cope with the process alone, they gave up on complying with the social distance rules.

We said that at least one should stay isolated in the house, so we kept my husband in a separate room. But I had a hard time when taking care of a child and cooking. I gave up. Four days later, my daughter and then my husband had a fever. This time, I had to care for both of them. (P9)

Some of the pregnant women stated that, when they were positive, they followed very strict social distance rules, living in separate houses from their family in order not to infect their children and spouses, and this situation drained them emotionally:

I had a three-and-a-half-year-old boy. When COVID-19 first came out, we were separated for a month. This worn me out. As a mother, going into quarantine and staying away made me sad. We went into different the houses and spent the quarantine alone at home. (P7)

COVID-positive pregnant women who had to live in the same house with family members during quarantine stated that they were forced to live in separate rooms.

I was in my own room, and my mother was in her own room. We had a corona in September. The weather was hot, so my husband and children lived on the balcony. (P5)

Coping Methods

To cope with the COVID-19 infection, pregnant women exhibited avoidance behaviors from social media in order not to receive news about infected patients. Social support and consuming foods that increase the immune system have been effective in coping with COVID-19 infection. Additionally, the presence of antibodies due to the COVID-19 infection had a relaxing effect.

Social Support

During the quarantine process, pregnant women stated that they received support from their spouses, family, friends, neighbors, nurses, and doctors.

My husband's family was extremely helpful. Everyone sent food for ten days, so I didn't have to cook at all. (P9)

Our family doctor was really involved and called us almost every day. Every day inquired about whether I had any symptoms. (P6)

My friends were very helpful, and my phone was never turned off. They brought food with them. When our doorbell rang, I was overjoyed. (P12)

My biggest supporter was my neighbors. Every day, a my neighbor cooked and sent enough food for everyone in the house. (P5)

Strengthening Immunity

Pregnant women reported that they consumed certain foods and beverages (onions, garlic, pickles, bananas, bone broth, and thyme infusion) more frequently and took nutritional supplements to promote healing.

I definitely drank thyme tea every day and even tried giving my child a spoon or two. I often made soup for bone broth… We also ate plenty of raw garlic and onions. I cut the onion and smell it, … as I drew it, I felt it bitter and smell. The smell came immediately on the third day . . . (P13)

After I got a corona, my doctor started vitamin C. After selenium, propolis and zinc, I use magnesium, omega 3 and vitamin D. (P6)

Beliefs and Prayer

Pregnant women reported praying about their worries about the illness and emphasized their belief in destiny.

I am not going to imprison myself. Now I say protection is from Allah. … I believe it (fetus) is not affected . . . (P14)

Avoidance From Social Media News

The majority of pregnant women reported that social media had a negative effect on them.

. . . Maybe it's ridiculous, but I don't follow-up posts on social media because I'm badly affected. I'd rather stay away. (P6)

Thought of "I survived COVID"

Some said that once they were free of the disease, their fears caused by the uncertainty vanished.

I had my turn. I have antibodies, I say nothing will happen, and I subconsciously relax myself. (P14)

Perinatal Period Changes

Some of the pregnant women stated that they were affected by both health services and social and economic changes. In some, prenatal care visits were interrupted. Some of them had to choose the hospital accordingly in order not to be alone in the birth, so there was an increase in health expenditures.

Postponement of Tests and Examinations

Pregnant women who had to stay at home during the quarantine-experienced disruptions and delays in some important tests and follow-ups during pregnancy.

As the disease intervened, my glucose screening test was delayed to the 28th week. (P8)

I bled for 3 days during the quarantine period. Frankly, I thought the baby had gone, and I was scared. I could not go to the doctor either. (P14)

Changes in Hospital Selection for Delivery

Most of the participants planned to attend private hospitals with maternity units rather than public hospitals, due to the risk of re-infection with COVID-19 in the hospital at birth.

Although it is a private hospital, the hospital is the biggest risk environment, and COVID is everywhere. Therefore, I am afraid of being caught again in that environment. (P14)

Fear of Being Alone at Home

Most of the pregnant women (n=10) stated that they feared being left alone during the delivery because of the possibility of their relatives not being admitted to the hospital.

I guess they will not be able to let my husband be with me when giving birth. I will give birth alone. It makes me sad that no one is with me. (P15)

Increases in Health Expenditures

Because of the risk that hospitals would not accept them for the delivery, they chose private health facilities, rather than public pandemic hospitals, despite the extra financial burden.

We preferred a hospital (private) without a COVID clinic. (P6)

Worries About Postpartum Visits

Some expressed concern about the inability to conduct cultural traditions, such as mother-baby visits after childbirth. For some, this concern stems from their inability to restrict the number of visitors at hospital, and for others, and the inability to admit any visitors to their homes.

They will want to see my baby and buy a gift, but I will not be able to accept anyone in my house. I am worried that we will not be able to meet many people for a very long time. (P9)

I worry if my husband's friends come to visit at the hospital. (P11)

DISCUSSION

In this study, the experiences of women infected with COVID-19 during the pandemic were examined under four main themes "psychosocial health, change in daily routines on quarantine days, coping methods, and perinatal period changes", and it was determined that pregnant women experienced many difficulties while infected with COVID-19.

Psychosocial Health

Most of the pregnant women reported experiencing sadness and desperation if their spouses were positive simultaneously, and experiencing the fear of transmitting the disease to their children and elderly family members. Similarly, a review found that pregnant women's main concerns were their elderly relatives, children, and unborn babies, respectively, during the COVID-19 pandemic (17). They experienced worry and anxiety concerning issues such as who would care for their children if something bad happened to them, and the possibility of catching the disease again in a more severe form during pregnancy. It has been reported that uncertainty and doubt increase fear and anxiety in pregnant women (7). In our study, pregnant women expressed their uncertainties about their baby's health using the "closed box" analogy. An analogy that supports this statement of pregnant women is the authors' definition of women's experiences of becoming pregnant during COVID-19 as being clouded by the unknown (18). Some studies have reported that pregnant women experience feelings such as fear and anxiety about their babies', their families' and their own health, even if undiagnosed with COVID-19 during the pandemic process (2,6,10,19-22). Healthcare professionals must increase attention toward the mental health of pregnant women diagnosed with disease during crisis processes, such as the COVID-19 pandemic, and to focus on interventions to increase psychological resilience (10,21).

Changes in Daily Routines

At the time of data collection after being diagnosed with COVID-19, pregnant women were required to remain in home quarantine for 14 day; two of the pregnant women regarded this process as a short break from work and evaluated it as a positive experience.

However, pregnant women sharing the common areas at home with their family members stated that they were tired by the extra effort needed for cleaning and hygiene practices. Those who felt extreme tiredness due to illness could not spare enough time for their children. During the quarantine period, some tried protecting their spouses by keeping social distance and living in separate rooms. However, some stopped applying social distancing rules, being unable to cope with multiple tasks such as housework, childcare, and cooking. Only two pregnant women evaluated the quarantine process positively, while the others reported experiencing a difficult and troublesome process. Qualitative studies conducted in Turkey also reported that the pandemic affected adaptation to pregnancy both negatively and positively (23), and changed daily routines (7). Our findings reveal that, to facilitate their work, pregnant women in quarantine at home need psychological and physical support.

Coping Methods

Social support systems have an important place in individuals' lives. Interpersonal relationships play an important role in maintaining health by providing emotional, material, and cognitive assistance to individuals (2). In our study, it was determined that pregnant women received social support from their families, colleagues, and neighbors during the quarantine process. Pregnant women with strong social support systems stated that they felt psychologically stronger due to communication established via phone. Additionally, they reported that the information received by phone from health personnel and the doctor had a significant effect on their state of mind. Similarly, in a Swedish qualitative study, pregnancy information gained through interviews with midwives over the internet was considered beneficial. However, physical visits continued in maternity care in Turkey, and telehealth services were not substantially employed during the pandemic period (18).

Some pregnant women stated that they use certain foods and nutritional supplements such as onions and garlic, which they believe will boost their health and strengthen their immunity. Some pregnant women emphasized spiritual aspects, praying and having faith that nothing bad would happen to their baby. Some believed that antibody production because of the disease would prevent re-infection, while others considered that developing the disease early in pregnancy is beneficial. The majority of pregnant women avoided social media news, to avoid its negative emotions and effects. Similar results were obtained in other qualitative studies conducted in Turkey (7,23).

Perinatal Period Changes

Access to health care is one of the most significant challenges facing pregnant women during the pandemic

(24). In our study, pregnant women stayed at home during the quarantine period, or until the test turned negative, causing delays in some antenatal tests and examinations. Mothers need to know that the baby is well and to have regular check-ups and examinations, and their failure to do so increases anxiety and feelings of neglect (18). In line with these findings, various studies found that during the pandemic period, canceled pregnant women's appointments led to inadequate and low -quality antenatal service (24,25).

Pregnant women tended to choose private hospitals to provide assurance in this regard, to avoid the risk of being re-infected in public hospitals, or risking being refused access to public hospitals for delivery. This situation has increased economic costs in pregnancies during the pandemic period. Kajfy et al. (26) drew a similar conclusions in their study. Due to the pandemic, in some health institutions in Turkey, as in many countries, there were restrictions on the participation of spouses in perinatal health services and the presence of companions during the birth and postpartum period. For this reason, pregnant women in our study worried about being alone at birth and in the early postpartum period. In some studies, because of the perceived risk of transmission of COVID-19 infection in hospitals, it was determined that pregnant women postponed their examinations, minimized their hospital stays (10,19,24), and were more likely to request cesarean delivery (7,8). Nurses should be mindful of pregnant women's support needs and be aware that local and national limits on visitors and companions can increase the support needed (5).

Some pregnant women stated that they were worried about neglecting postpartum social rituals (such as home visits, giving gifts for the baby) due to the pandemic, and some expressed sadness at this. Kumari et al. (2) found negative influences on the mental well-being of women in the perinatal period when they could not fulfill cultural practices due to the pandemic. An Australian qualitative study also stated that they were worried about not being able to share the joys of pregnancy with their loved ones (27).

This study had some limitations. Interviews rely on memory recall, since the quarantine processes of pregnant women had ended before the data collection process. Additionally, the study included pregnant women infected with COVID-19 in different trimesters. Video conference interviews were planned, but all of the pregnant women preferred to conduct interviews over the phone, and it was impossible to observe their facial expressions and emotions during the interview. As only a limited number of pregnant patients infected with COVID-19, our results cannot be generalized to all populations. Our study contributes to the literature by revealing the experiences of women infected with COVID-19 during the pandemic process through in-depth interviews.

CONCLUSION

COVID-19 and quarantine processes have negatively affected pregnant women's psychosocial health by causing worry, anxiety, and fear. Pregnant women were first concerned about the health of their babies, followed by their children and family members. Quarantine practices were psychologically and physically exhausting during their illness, and negatively affected their well-being. In this process, they were supported in their daily work (housework, cooking, child care) by family, friends, and spouses, including via telephone communication The disruption of perinatal controls and examinations during the quarantine period increased the anxiety over risks to the unborn baby. This situation and the uncertainties experienced were defined as "closed box" by the pregnant women. The phone support provided by nurses, midwives, and physicians (routine antenatal cares, psychological, birth preparation classes, breastfeeding consultation) became important. To reduce pregnant women's anxiety and fear in case of possible future contagious diseases and quarantine applications, it is recommended to conduct and support perinatal services and training as e-health (i.e., phone, internet) services and to establish follow-up steps to facilitate remote follow-up systems.

ETHICS

Ethics Committee Approval: Ethical permission was obtained from the İzmir University of Economics Ethics Committee for the study (approval no: B.30.2.İEÜSB.0.05.05-20-099, date: 21.12.2020), and the T.C. The ministry of Health's COVID-19 Scientific Research Assessment Commission granted the requisite approval.

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Authorship Contributions

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

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Research

Evaluation of Children with Secondary Osteoporosis: A Single-center Experience

Sekonder Osteoporoz Tanılı Çocukların Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Objective: Children with chronic diseases are at a risk of inadequate bone mineralization due to the effects of the primary disease and/or treatment. The aim of this study was to evaluate the clinical characteristics and treatment responses of patients with secondary osteoporosis.

Methods: Forty-four patients with chronic diseases who had bone mineral density (BMD) Z-score of ≤-2.0 on the dual-energy X-ray absorptiometry (DXA) were included.

Results: Age at diagnosis of osteoporosis was 9.2±4.9 years (1.4-17.7 years). Chronic disease groups were defined as gastrointestinal (29.5%), neurological (22.7%), hematologic (18.2%), inborn errors in metabolism (11.4%), rheumatologic (9.1%), and renal (9.1%). The rate of receiving steroid treatment was 63.6%. DXA Z-score was -2.8±0.9. The fracture frequency in the long bones was 20.5%. Bisphosphonate (BP) treatment was given in 34.1% (n=15) of the patients. BP was the most commonly used in neurological diseases (50%). A significant difference was found between the initial and final DXA Z-scores in BP patients (-3.3±1.0 and -2.4±0.9; p=0.004).

Conclusion: In our study, a heterogeneous group of chronic systemic diseases was evaluated, and BP treatment provided a significant improvement in BMD. Further prospective studies are still required in which clinical and radiological improvements are evaluated in large groups of patients.

Keywords: Bisphosphonates, secondary osteoporosis, pediatric endocrinology

ÖZ

Amaç: Kronik bir hastalık nedeniyle izlenen çocuklar, hastalığın etkileri ve/veya tedaviye bağlı olarak yetersiz kemik mineralizasyonu riski taşımaktadırlar. Kronik hastalıklara bağlı osteoporozu olan hastaların klinik özelliklerinin ve tedavi yanıtlarının değerlendirilmesi amaçlanmaktadır.

Gereç ve Yöntem: Kronik hastalık nedeniyle izlenen, dual-enerji X-ışını absorbsiyometri (DXA) ile vertebra kemik mineral yoğunluğu (KMY) boy yaşına göre Z-skorunun ≤-2.0 olan 44 hasta çalışmaya alındı.

Bulgular: Osteoporoz tanı yaşı 9,2±4,9 yıl (1,4-17,7) idi. Kronik hastalık grupları gastrointestinal (%29,5), nörolojik (%22,7), hematolojik (%18,2), doğumsal metabolik (%11,4), romatolojik (%9,1) ve renal (%9,1) olarak belirlendi. Steroid tedavisi alma oranı %63,6 idi. DXA Z-skoru -2,8±0,9 idi. Uzun kemiklerde kırık oranı %20,5 idi. Hastaların %34,1'inde (n=15) bifosfonat (BP) tedavisi verilmişti. BP, en sık nörolojik hastalıklarda (%50) kullanılmıştı. BP alanlarda başlangıç ve son DXA Z-skorları arasında anlamlı fark saptandı (-3,3±1,0 ve -2,4±0,9; p=0,004).

Sonuç: Çalışmamızda farklı hastalık gruplarından heterojen bir grup değerlendirilmiş olup BP tedavisinin KMY'de anlamlı bir düzelme sağladığı görülmüştür. Her hastalık grubu için büyük gruplarda klinik ve radyolojik düzelmenin birlikte değerlendirildiği prospektif çalışmalara gereksinim vardır.

Anahtar Kelimeler: Bifosfonat, sekonder osteoporoz, pediatrik endokrinoloji

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INTRODUCTION

Osteoporosis is characterized by microarchitectural deterioration of bone tissue and low bone mass. According to the pediatric position statements of the International Society of Clinical Densitometry (ISCD), osteoporosis in children is defined by the presence of a clinically significant fracture or a significant fracture history and a low bone mineral density (BMD) (1-3). The use of ISCD criteria to define osteoporosis in children has been challenged, nowadays. Hence, taking into account underlying conditions and fracture risk, signs of a monogenic disorder, glucocorticoid (GC) use, and clinical features of fracture are accepted as a more contemporary view (4).

Osteoporosis is classified as primary and secondary osteoporosis (SO). There are many significant causes of bone fragility causing primary osteoporosis (PO) such as osteogenesis imperfecta (OI). Nonetheless, osteoporosis in children is usually secondary to chronic systemic illness or its treatment. Using GCs reduces bone strength and results in increased fragility, and consequently fractures (1).

Bisphosphonates (BP) are widely used for treating osteoporosis, due to their effect on preventing the loss of bone density (1). Some report that short-term use of BPs appears well-tolerated. The evidence for BPs in SO treatment remains inadequate. For this reason, more studies have been planned that focus on the efficacy and safety of BPs in SO treatment in children.

In this study, our aim was to describe the characteristics of our patients with SO who had different etiologies for their bone fragility and to define the treatment responses to BPs.

METHODS

A retrospective observational study was performed in 132 patients with pediatric osteoporosis in the Pediatric Endocrinology Unit of the İstanbul University, İstanbul Faculty of Medicine.

The anthropometric, clinical, laboratory, and radiologic data were obtained from the patient records. The osteoporosis cohort included 88 patients with PO (n=83 OI, n=4 osteoporosis pseudoglioma syndrome, n=1 spondyloocular syndrome), and 44 patients with SO. Patients with SO were referred from the various departments of pediatrics who were in the follow-up due to different types of chronic diseases.

The study was approved by the Local Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 08, date: 02.04.2021).

Pubertal development was assessed according to Tanner's stages. Weight and height were measured in all subjects, using a wall-mounted calibrated Harpenden Stadiometer (Holtain Ltd.) and electronic scale (sensitivity to 0.1 kg). Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m^2). All measurements were expressed as standard deviation scores (SDS) according to national standards (5).

ISCD criteria were used to define osteoporosis:

i. One or more vertebral compression fractures in the absence of high-energy trauma or local disease, regardless of the BMD Z-score.

ii. The presence of BMD Z-score ≤-2.0 and a clinically significant fracture [in the absence of vertebral fractures (VF)].

Clinically significant fractures were defined as follows:

a) Two or more long bone fractures by the age of 10 years;

b) Three or more long bone fractures at any age up to 19 years (3).

Intravenous (IV) BP (pamidronate) was applied (3 mg/kg/dose) and repeated every 3-6 months (6). Oral alendronate was administered at a dose of 70 mg/week.

Oral vitamin D (1200 U/day) and calcium (Ca) supplementation (500-1000 mg/day) were used at recommended doses (7). The doses were adjusted according to Ca and 25-hydroxyvitamin D [25(OH)D] serum levels. 25(OH)D below 20 ng/mL was accepted as 'deficiency', and between 21-29 ng/mL was considered 'insufficiency'.

Those with fractures and/or compression fractures of the vertebrae were primarily treated with BPs in addition to vitamin D and Ca.

Biochemical Assays

The quantitative determination of Ca in the serum was studied with the photometric method (Roche/Hitachi Cobas C system). The range of measurement of this test is 0.8-20.1 mg/dL. The quantitative determination of phosphorus (P) in the serum was also done by the photometric method (Roche/Hitachi Cobas C system). The measurement range of the test is 0.31-20 mg/dL. Alkaline phosphatase was measured using the photometric method (Roche/Hitachi Cobas C system). The measuring range of the test was 5-1200 U/L. Parathyroid hormone was measured by the electrochemiluminescence method (Modular Analytical E170 device). The range of measurement of the test was 1.2-5000 pg/mL. 25(OH)D was measured using the high-performance liquid chromatography.

Imaging

BMD was evaluated using DXA with a Hologic QDR 4500A Fan Beam X-ray Bone Densitometer (Hologic, Bedford, MA) and analyzed using software version 12.3. BMD results are presented in Z-scores, which are in SDS relative to mean values for equipment-specific age and sex-matched national data (8). Volumetric BMD was calculated from the spine (L1-L4). The formula of Carter et al. (9), which is bone mineral content/area1.5 was used.

Statistical Analysis

The data were analyzed using the SPSS for Windows software package, version 21.0 (SPSS, Chicago, IL). Data were tested for normality distribution using the Shapiro-Wilk test. Descriptive statistics were used to summarize all variables of interest. Categorical data were reported as frequencies and percentages. Continuous variables are expressed as mean ± SDs. A nonparametric t-test was used for the comparison of numeric and χ^2 tests for categorical variables. Pearson or Spearman analyses were used to determine the correlations between the clinical parameters. A p-value of <0.05 was considered as statistically significant.

RESULTS

In this study, SO constituted 33.3% (n=44) of our pediatric osteoporosis cohort. The clinical data of the patients with PO were reported previously by our group (10-12). Patients with SO (22 females) who were followed up with various chronic diseases and referred to endocrinology for the monitorization of endocrine side effects related to primary condition and/or treatments, were enrolled.

Those with BMD Z-scores ≤-2.0 on the DXA (lumbar spine) and/or patients with history of significant fractures, constituted the study group (according to the criteria described above).

The mean age of diagnosis of the primary disease (chronic disease) was 3.4±3.9 years (median 2.4, range: 0.0-15.3 years) in our SO cohort. The mean age of diagnosis of SO was 9.2±4.9 years (range:1.4-17.7 years). Primary chronic diseases were classified as gastrointestinal (29.5%), neurologic (22.7%), hematologic (18.2%), inborn errors in metabolism (11.4%), rheumatologic (9.1%), and renal (9.1%) (Figure 1). The distribution of chronic diseases according to the primary etiology is demonstrated in Table 1. The ratio of those receiving GC treatment was 63.6%. The mean values of height and BMI SDS at admission to endocrinology were -1.4±1.4 and -0.3±1.8, respectively. The ratio of short stature (height <-2.0 SDS) was 30.2%. Twenty-seven patients (61.4%) were prepubertal, at admission. Only two patients (2 female) had pubertal delay (4.5%), and their primary diseases were thalassemia major (with bone marrow transplantation) and epilepsy (due to tuberous sclerosis). Two patients had VF (4.5%) and eight patients (18.1%) had complaints of back pain, in the cohort.

The mean value of the DXA Z-score was -2.8±0.9 and 20.5% of the patients had a history of long bone fractures. There was no correlation between the type of chronic disorder and the presence of long bone fractures (r=0.03, p=0.847) and no correlation with the number of long bone fractures (r=0.075, p=0.848). Vitamin D deficiency was detected in 10 patients at admission (22.7%), and it was most frequently encountered in patients with gastrointestinal disorders.

The mean time period for the follow-up of these patients in the endocrinology unit was 4.6±3.3 years.

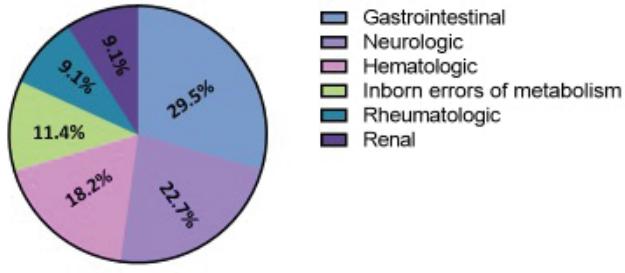

Figure 1. The ratio of chronic diseases in the secondary osteoporosis cohort

Table 1. The distribution of primary chronic diseases causing secondary osteoporosis

Disease group	n (%)	The type of primary disease
Gastrointestinal diseases	13 (29.5)	Chronic liver disease (n=8), Crohn disease (n=3), celiac disease (n=1), chronic pancreatitis (n=1)
Neurologic diseases	10 (22.7)	Duchenne muscular dystrophy (n=5), tuberous sclerosis and epilepsy (n=1), epilepsy (n=1), lomber meningomyelocele and hydrocephaly (n=2), cerebral palsy (n=1)
Hematologic diseases	8 (18.2)	Malignancy (n=4), bone marrow transplant (n=2), thalassemia major (n=1), chronic immune thrombocytopenic purpura (n=1)
Inborn errors of metabolism	5 (11.4)	Galactosemia (n=2), glycogen storage disease (n=1), fructose 1,6 bisphosphotase deficiency (n=1), lysinuric protein intolerance (n=1)
Rheumatologic diseases	4 (9.1)	Juvenile idiopathic arthritis (n=4)
Renal diseases	4 (9.1)	Nephrotic syndrome (n=2), renal tubular acidosis (n=1), chronic renal failure secondary to hemolytic uremic syndrome (n=1)

Fifteen patients (34.1%) received BP therapy (pamidronate n=14, zoledronate n=1, and alendronate n=1). One patient was transferred to zoledronate due to allergic reactions to pamidronate treatment. No other complications besides flu-like symptoms and mild hypocalcemia were observed during the follow-up. Pamidronate was used in a dose of 1-3 mg/kg (IV) in a 3-6-month period. The mean cumulative dose was 12.8±8.7 mg/kg (range: 3.0-33.0 mg/kg). Fifty percent of the patients treated with BP were in the neurological disorder group.

BMD Z-scores of the patients who received BPs at admission and last evaluation were -3.3±1.0 and -2.4±0.9, respectively (p=0.004). BMD Z-scores of the patients who do not receive BP therapy at admission and at the last evaluation were, -2.5±0.8 and -2.5±1.1, respectively (p=0.075).

The clinical characteristics and response to BP therapy in patients with SO are demonstrated in Table 2.

DISCUSSION

The life expectancy of patients with chronic systemic diseases has been significantly increased; therefore, long-term morbidities such as osteoporosis have become an important issue (2). In this study, we described the characteristics of patients with SO with various chronic diseases and the responses to BP therapy.

Most of the chronic diseases or their treatment affect BMD and cause fractures. Hence, osteoporosis in children is usually secondary to chronic illness or its treatment (1). In our pediatric osteoporosis cohort, SO constituted only one-third of the cases. This may be explained by well care of the primary disease, prevention of immobilization, abstaining from high-dose and long-term GCs or more frequent referral of PO to a tertiary center.

Table 2. **The clinical characteristics and response to bisphosphonate therapy in patients with secondary osteoporosis**

Clinical characteristics of the patients		
	At admission	**At the last evaluation**
Age (years)	9.2±4.9	13.5±4.5
Height SDS	-1.4±1.4	-1.5±1.4
BMI SDS	-0.3±1.8	0.2±2.5
Response to BP therapy		
	DXA Z-score at admission	**DXA Z-score at the last evaluation**
BP therapy (+) (n=15)	-3.3±1.0*	-2.4±0.9*
BP therapy (-) (n=29)	-2.5±0.8	-2.5±1.1

*Defines p<0.05
BP: Bisphosphonate, SDS: Standard deviation scores, BMI: Body mass index, DXA: dual-energy X-ray absorptiometry

The most frequent conditions that cause SO are inflammatory diseases (causing malabsorption), myopathies such as Duchenne muscular dystrophy, malignancies, thalassemia, immobilization, and hypogonadism (1,2,13). In our cohort, approximately one -third of the patients had gastrointestinal disorders causing SO. This is particularly related to the additive effects of malabsorption of lipid-soluble vitamins causing 25(OH)D deficiency, despite the suggestion of routine vitamin supplements by gastroenterologists. In accordance with this, 25(OH)D deficiency was also most frequent in the gastrointestinal disorder group, in our cohort.

Systemic GCs increase bone resorption, inhibit bone formation, and consequently decrease peak bone mass (14). Using oral GCs for more than 3 months and greater than 5-7.5 mg/day of prednisone (or equivalent), increases the fracture risk (15). GC excess adversely affects muscle mass/function, causing myopathy and increased risk of falls, which is another risk factor for fractures (16). In our cohort with chronic diseases, more than half of the patients had received or were still receiving GC therapy.

Some medications adversely affect bone quality due to altered Ca and 25(OH)D metabolism, due to the induction of the cytochrome P450 enzyme by the anticonvulsants such as phenytoin, phenobarbital, and carbamazepine, increase the risk of fragility fractures. Therefore, Ca and vitamin D must be supplemented in patients who use these medications (16,17). In our unit, oral vitamin D and Ca supplementation were offered at recommended doses, and in cases, with deficient vitamin D higher doses were applied. Nonetheless, the type of drugs used for primary disease, compliance problems due to multiple drug use, immobilization and inadequate exposure to the sun, and malabsorption of lipid-soluble vitamins may all affect the Ca and vitamin D status of these patients.

Patients who have recurrent fractures or having orthopedic surgery that requires better bone quality, with low BMD will require treatment (16,18). In immobilized children, the estimated prevalence of fragility fractures was 20%. Indeed, immobilization is mostly a problem for children with neurologic disorders, and they constituted the second most frequent cause of SO in our cohort. SO is a severe complication in neurologic diseases such as, muscular dystrophies, and cerebral palsy (19). The ratio of using BPs was highest in the patients with neurologic diseases in our

study, most likely due to the above-mentioned problems of mobilization.

The main manifestation of both PO and SO is VFs, hence routine screening is necessary. VFs can often be asymptomatic and recognized on routine screening (16). Lateral spine radiographs can be of limited quality when diagnosing VFs, and radiation exposure is the main drawback to its use. Symptoms of back pain may be an alerting sign for the VFs. Two patients had VF (4.5%) and eight patients (18.1%) had complaints of back pain, in our cohort. However, some mild cases of vertebral compression may be missed upon the infrequent application of X-rays due to the fear of radiation exposure.

BPs inactivate/inhibit osteoclast formation and act as an anti-resorptive agent. They improve the acquisition of bone mass, reducing the fracture rate in some forms of osteoporosis (19). Although, it has been now replaced in most centers by the more potent zoledronate, pamidronate has been used most extensively up to date. Oral BPs, mainly alendronate and risedronate, are less frequently used in children. IV and oral BPs increase BMD in children, as confirmed in other previous studies reporting the use of BPs in SO (2,16,20). In our cohort, about one-third of the patients were treated with BPs. We have observed that the BMD Z-score of those receiving BPs was significantly higher compared with those who do not receive treatment.

Several conditions have been associated with SO, mostly the use of GCs, systemic inflammation, hypogonadism, and immobility. Children with these conditions should be screened with DXA and lateral spine images at diagnosis and should be followed with repeated assessments (16).

CONCLUSION

In our study, a heterogeneous group of chronic systemic diseases was evaluated and we have seen that BP therapy provided a significant improvement in BMD Z-scores and clinical findings. Furthermore, prospective studies must guide clinical practice in children with SO, as all medications used for pediatric osteoporosis are still based mainly on clinical experience.

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ETHICS

Ethics Committee Approval: The study was approved by the Local Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 08, date: 02.04.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Z.Y.A., F.B., Ş.P., A.P.Ö., R.B., F.D., Concept: Z.Y.A., F.B., F.D., Design: Z.Y.A., F.B., Ş.P., A.P.Ö., R.B., F.D., Data Collection or Processing: Z.Y.A., F.B., A.P.Ö., R.B., Analysis or Interpretation: Z.Y.A., F.B., Ş.P., F.D., Literature Search: Z.Y.A., Writing: Z.Y.A., F.B., Ş.P., F.D.

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Research

Kawasaki Disease: 10-year Single-center Experience: Analysis of Clinical and Laboratory Findings with Treatment Approaches

Kawasaki Hastalığı: Tek Merkezde 10 Yıllık Deneyim: Klinik ve Laboratuvar Bulgularının Tedavi Yaklaşımları ile Birlikte Analiz Edilmesi

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ABSTRACT

Objective: Kawasaki disease (KD) is an acute febrile multisystem disease affecting children between 6 months and 5 years. Coronary artery involvement (CAI) is the most threatened complication of this disease. Therefore, suspicion and early diagnose of the disease is critical. Principal and additional findings are used for diagnosis accompanied by laboratory findings. We evaluated the patients who had the diagnosis and treated for KD at our center.

Methods: Forty-five patients who were evaluated between 2012-2022 with the diagnosis of KD were evaluated retrospectively in our study. Intravenous immunoglobulin (IVIG) administration time, and presence of principal, and additional findings were recorded. Echocardiographic and laboratory findings were also recorded for the study.

Results: Male patients were in predominace, average age was 2 years. Coronary artey involvement was present in 20% and IVIG resistance in 17.8% of the patients. Changes in the oral mucosa and lips were less frequent in the patients with CAI (+), and perineal desquamation was more frequent with IVIG resistance (p=0.039, p=0,033, respectively). All the patients were treated before 10 days (p>0.05) and a second dose of IVIG was administered to 2 patients on the 12th day.

Conclusion: KD should be considered for the patients with longlasting fever, which cannot be explained with other reasons in children under 5 years of age. The relationship between the principal and additional findings with the presence of CAI and IVIG resistance were not mentioned in the literature previously. The similarity of laboratory findings in the groups suggests that laboratory findings may not always guide us about the course of the disease. Although KD may have severe complications, with timely and accurate diagnosis and treatment, the prognosis is good in general.

Keywords: Kawasaki disease, children, coronary artery, intravenous immunoglobulin

ÖZ

Amaç: Kawasaki hastalığı (KH), 6 ay ile 5 yaş arasındaki çocukları etkileyen akut seyirli, ateşli multisistem bir hastalıktır. Koroner arter tutulumu (KAT) bu hastalığın en tehdit edici komplikasyonudur. Bu nedenle hastalıkta şüphe ve erken teşhis çok önemlidir. Temel ve ilave bulgular, laboratuvar bulguları ile birlikte tanı için kullanılır. Merkezimizde KH tanısı alan ve tedavi edilen hastaları değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmamızda 2012-2022 yılları arasında KH tanısı ile değerlendirilen 45 hasta retrospektif olarak değerlendirildi. İntravenöz immünoglobulin (İVİG) uygulama zamanı, tanısal ve ek bulguların varlığı kaydedildi. Çalışma için ekokardiyografik bulgular ve laboratuvar bulgular da kaydedildi.

Bulgular: Erkek hastalar çoğunlukta idi, yaş ortalaması 2 idi. Hastaların %20'sinde koroner arter tutulumu, %17,8'inde İVİG direnci mevcuttu. KAT (+) olan hastalarda oral mukoza ve dudak değişiklikleri daha az, İVİG direnci olan hastalarda perineal deskuamasyon daha sıktı (sırasıyla p=0,039, p=0,033). Hastaların tamamı 10. günden önce tedavi gördü (p>0,05) ve 2 hastaya 12. günde 2. doz İVİG uygulandı.

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ÖZ

Sonuç: Beş yaş altındaki çocuklarda başka nedenlerle açıklanamayan uzun süreli ateş varlığında ayırıcı tanıda KH düşünülmelidir. KAT ve İVİG direncinin varlığı ile temel ve ek bulgular arasındaki ilişki literatürde daha önce belirtilmemiştir. Laboratuvar bulgularının gruplarda benzer olması, laboratuvar bulgularının hastalığın seyri hakkında bize her zaman yol göstermeyebileceğini belirtmektedir. KH ciddi komplikasyonlarla sonuçlanabilse de zamanında ve doğru tanı ve tedavi ile genellikle prognozu iyidir.

Anahtar Kelimeler: Kawasaki hastalığı, çocuklar, coroner arter, intravenöz immünoglobulin

INTRODUCTION

Kawasaki disease (KD) is an acute febrile multisystem disease of affecting children between 6 months and 5 years (1). It is characterized by a vasculitis effecting medium sized muscular arteries. The disease first was reported in 1967 by a Japanese pediatrician Tomisaku Kawasaki (2). Since then, it has been recognized in many countries all around the world and nowadays it is the leading cause of acquired heart disease in children who are living in developed countries (1,3). The incidence of KD is approximately 330.2/100,000 in Japan and 19.7/100,000 in the USA (2). From Turkey, there has been limited published data therefore we only have the knowledge that it constitutes 9% of the childhood vasculitis and it is the second most prevalent vasculitis in Turkey (4).

The ethiopatogenesis of the illness is still unknown. Infectious agents and immunological abnormalities are blamed (1). Twins have an increased risk of KD; therefore, genetic tendency is thought to play an important role in the ethiopatogenesis (5).

Coronary artery involvement is the most threatened complication of this disease (6). Therefore, suspicion and early diagnose of the disease are critical. There is not a specific diagnostic test to determine the diagnosis of KD (6). The diagnosis of KD is made by using clinical criteria and excluding the other clinical diseases such as viral, bacterial infections, toxin-mediated and hypersensitivity reactions, and rheumatic disease (2,7). Longlasting fever, which is resistant to antipyretic drugs, is the main complaint of this illness. There are 5 principal findings for the diagnosis of KD. These findings are (1,2,5);

a) Bilateral non exudative conjoctival hyperemia,

b) Mucosal changes in the lips and oropharynx, including hyperemia of the oral mucosa with red and dry lips accompanied with fissuring and redness of the tongue like strawberry,

c) Polymorphic rash-like maculopapular diffuse erythema, urticarial exanthema, and erythema multiforme-like lesions without vesicle or bullae formation except bacillus Calmette-Guérin (BCG) inoculation site,

d) Changes in the peripheral extremities: Erythema and edema of the hands and feet,

e) Cervical lymphadenopathy, which is unilateral, firm, non-fluctuant, and painful with a size bigger than 1.5 cm.

There are two types of KD diagnosis: complete and incomplete forms. The complete form consists of fever longer than 5 days and the presence of at least 4 of the 5 principal findings. The incomplete form consists of fever duration shorter than 5 days accompanied with 2 or 3 of the principal findings, supported by laboratory or echocardiographic findings (8,9).

Laboratory findings are; leukocytosis with a shift to left, elevation of erythrocyte sedimentation rate, and C-reactive protein (CRP). The elevation of platelets (PLT) (nearly 700,000 up to 1,000,000/mm^3), decrease in hemoglobin (Hgb) levels, proteinuria, steril pyuria, elevation in transaminase levels, and elevation of biluribin levels (9-11).

Additional findings can be classified as: urethritis, hydrocele, phimosis, abdominal pain, vomiting, diarrhea, hydrops of gallbladder, paralytic ileus, pancreatitis, hepatitis, irritability, facial palsy, limb paralysis, febrile convulsion, encephalitis, and encephalopathy, behavioral changes, aseptic meningitis, sensorineural hearing loss, arthritis, arthralgia, sneezing, cough, pleural effusion, empyema, peri bronchial interstitial infiltrates, small pustules on the knees, elbows and buttocks (1,2,12).

KD has three phases. The findings and laboratory parameters differ between these three phases. The acute phase is the first two weeks of the illness when the patients have high fever accompanied with the other principal findings (2). The subacute phase begins after the fever resolves, and it prolongs for 4 weeks. During this phase, patients have desquamation of tips, arthralgia, and abnormal laboratory findings. The highest risk for coronary artery aneurysms (CAAs) is present in this phase. The convalescent phase is the second month of the illness. The risk of coronary artery involvement is lower during this period (2). The clinical symptoms are absent during this period. Patients are usually referred to hospital through the acute and subacute phases when it is the most risky period for coronary artery involvement (2).

Treatment consists of intravenous immunoglobulin (IVIG) with a dose of 2 gr/kg/day in one infusion of 10-12 hours and aspirin treatment at anti-inflammatory dosage (1,2,10,13). 10-15% of the KD children have recurrent or persistent fever at least 36 after the first dose of IVIG, which is defined as IVIG resistant (1,10,11,13). A second dose of IVIG is administered in for treatment. High-dose steriods were administered in case of repeated IVIG resistance. Prognosis is related with the presence of CAAs (11,13). We aimed to evaluate the patients who had the diagnosis and treated for KD at our center in our center.

METHODS

Patients who were treated for KD between 2012-2022 with the diagnosis of KD were evaluated in our study. Forty-five patients were included in the study. The study was performed retrospectively from their archieve folders. The duration of fever, presence of diagnostic, and additional findings were recorded. Echocardiographic findings were obtained from the archieve folders and hospital systems.

Echocardiographic Evaluation

All the patients included in the study were evaluated for the suspicion of KD at diagnosis. Cardiac functions, appearance and diameters of coronary arteries were examined for diagnosis. Coronary artery lesions were classified as perivascular echogenity, ectasia/dilatation, and aneurysm (14,15). Coronary arteries were grouped according to the AHA 2017 Guidelines. Z-score <2 was classified as normal; Z-score 2-2.5 or if initially <2 and a decrease in Z-score during follow-up ≥1 was classified as dilatation; Z-score 2.5-5 was classified as small aneurysm, Z-score 5-10 was classified as moderate, Z-score ≥10 was classified as large or giant aneurysm (16).

Laboratory Findings

Laboratory findings including erythrocyte sedimentation rate, CRP, white blood cells (WBC), Hgb, PLT, electrolytes (Na, K), and liver functions [aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin] were used for evaluating the patients.

Statistical Analysis

Statistical analyses were performed on NCSS 11 (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA). Frequency and percentage were used for categorical variables. Mean, standard deviation, median, minimum, and maximum values were used for continuous variables. The normal distribution of continuous variables was evaluated using the Shapiro-Wilks test. Non-normally distributed variables were compared using the Mann-Whitney U test for two independent groups. Fisher's Exact test and Fisher Freeman Halton test were used for categorical variables as required. The findings were in 95% confidance interval. P-values <0.05 were regarded as statistically significant.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2022-20-08, date: 17.10.2022) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from thethe patients.

RESULTS

Patients in the study revealed 28 male patients and 17 women patients. Male/female ratio was 1.64. Age of the patients was 3.16±2.76 years with a median of 2 years. Patients <1 years old were 9 patients, 1-5 years old were 27 and >5 years old were 9 patients. The age and gender of the patients between the groups in terms of coronary artery involvement and IVIG resistance were similar. There were 34 patients with complete KD and 11 patients with incomplete KD. Complete and incomplete KD were similar in terms of coronary artery involvement and IVIG resistance. Changes in the periferik extremities were present in 64.4%, polymorphic rash was present in 75.6%, conjoctival changes were present in 82.2%, changes in oral mucosa and lips in 82.2%, and lymphadenopathy in 42.2% of the patients. These findings did not show differences in terms of coronary artery involvement and IVIG resistance between the groups. WBC, PLT, AST, ALT, Hgb, and albumin did not differ between the patients with and without coronary artery involvement and IVIG resistance (p>0.05, for all). Coronary involvement was present in 20% of the patients. IVIG resistance was present in 17.8% of the patients (p>0.05) (Table 1).

When the patients were evaluated in terms of coronary artery involvement and IVIG administration time, IVIG administration time was similar between the patients with and without coronary artery involvement. IVIG was administered on the 7.8th day of the illness, and this time was similar in the patients with and without coronary artery involvement. A second dose of IVIG was administered on the mean 9.38th day to 8 patients who were IVIG resistant. This time period was similar to the patients without coronary artery involvement, whereas it was the 12th day in the patients with coronary artery involvement (p>0.05, for all) (Table 2).

Table 1. Sociodemographic findings, principal findings and additional findings according to the presence of coronary artery involvement

		Total (n=45) n (%)	Coronary artery involvement (-) (n=36) n (%)	Coronary artery involvement (+) (n=9) n (%)	p-value	IVIG responders (n=37) n (%)	IVIG resistants (n=8) n (%)	p-value
Gender	Male	28 (62.2)	21 (58.3)	7 (77.8)	[a]0.447	23 (62.2)	5 (62.5)	[a]1.000
	Female	17 (37.8)	15 (41.7)	2 (22.2)		14 (37.8)	3 (37.5)	
Age	Median (min-max)	2 (0.4-11)	2.2 (0.4-11)	1.8 (0.5-6.6)	[b]0.626	2.0 (0.5-10.8)	2.2 (0.4-11)	[b]0.755
	≤1 age	9 (100)	7 (77.8)	2 (22.2)	[aa]0.883	8 (88.9)	1 (11.1)	[aa]1.000
	1-5 age	27 (100)	21 (77.8)	6 (22.2)		22 (81.5)	5 (18.5)	
	≥5 age	9 (100)	8 (88.9)	1 (11.1)		7 (77.8)	2 (22.2)	
Complete/incomplete		34/11	29/7	5/4	[a]0.190	28/9	6/2	[a]1.000
Changes in peripheric extremities (+)		29 (64.4)	25 (69.4)	4 (44.4)	[a]0.245	25 (69.4)	4 (44.4)	[a]0.245
Polymorphic rash (+)		34 (75.6)	29 (80.6)	5 (55.6)	[a]0.190	26 (70.3)	8 (100)	[a]0.169
Conjoctival changes (+)		37 (82.2)	30 (83.3)	7 (77.8)	[a]0.651	32 (86.5)	5 (62.5)	[a]0.137
Changes in oral mucosa and lips (+)		37 (82.2)	32 (88.9)	5 (55.6)	[a]0.039*	29 (78.4)	8 (100)	[a]0.316
LAP (+)		19 (42.2)	16 (44.4)	3 (33.3)	0.712	15 (40.5)	4 (50.0)	0.704
Enduration of BCG (+)		6 (13.3)	6 (16.7)	0 (0)	[a]0.323	5 (13.5)	1 (12.5)	[a]1.000
Perineal desquamation (+)		5 (11.1)	4 (11.1)	1 (11.1)	[a]1.000	2 (5.4)	3 (37.5)	[a]0.033*
Sterile pyuria (+)		3 (6.7)	3 (8.3)	0 (0)	[a]1.000	2 (5.4)	1 (12.5)	[a]0.452
Albumin (g/dL)		3.3 (2-4.3)	3.1 (2-4.3)	3.4 (2.6-4)	[b]0.443	2.9 (2.3-4.3)	3.3 (2-4.3)	[b]0.137
ALT (IU/L)		38 (11-555)	34.5 (13-555)	41 (11-173)	[b]0.921	66 (11-555)	38 (11-555)	[b]0.146
AST (IU/L)		42 (16-419)	40.5 (16-419)	43 (21-226)	[b]0.629	57 (21-419)	42 (16-419)	[b]0.186
Hgb (g/dL)		9.9 (7.2-12.7)	9.9 (7.7-11.6)	9.9 (7.2-12.7)	[b]0.909	9.8 (9-11.4)	9.9 (7.2-12.7)	[b]0.552
WBC (x1000)/mm^3		15.6 (9.30-36.4)	15.6 (9.3-32.0)	20.0 (11.2-36.4)	[b]0.294	14.9 (11.4-23.7)	15.6 (9.3-36.4)	[b]0.603
PLT (x1000)/mm^3		454.0 (0.49-1134)	439.0 (120.0-1134)	626.0 (0.49-732)	[b]0.395	393 (202-732)	454 (0.5-1134)	[b]0.533
Na (mEq/L)		135 (130-141)	134 (130-141)	135 (131-138)	[b]0.275	132.5 (130-141)	135 (130-141)	[b]0.183

Hgb: Hemoglobine, LAP: Lymphadenopathy, Na: Sodium, PLT: Platelets, WBC: White blood cells, BCG: Bacillus Calmette-Guérin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IVIG: Intravenous immunoglobulin, min-max: Minimum-maximum
[a]Fisher Exact test, [aa]Fisher Freeman Halton test, [b]Mann-Whitney U test
*p<0.05

The laboratory parameters for evaluating the risk factors for coronary artery involvement according to the Harada scoring system were similar in terms of coronary artery involvement (p>0.05, for all) (Table 3).

DISCUSSION

KD is an aute, systemic, febrile vasculitis that occurs usually in infancy and is the most common reason for coronary artery disease during childhood (14). KD is more prevalent in male patients (2). Approximately 85% of the patients were <5 years old with an average of 2 years of age (12). Patients in our study revealed a predominance of male patients with a ratio of 1.64 in concordance with the literature. Scott et al. (17) performed a study and declared that the mean age of the patients with KD was 3 years (range 0.2-16 years). The age intervals of the patients in our study was between 0.4-11 years with a median of 2 years. Most of the patients were between 1-5 years of age but also there are 7 patients older than 5 years in our study.

Principal findings occur approximately with a ratio of 80-85% in patients with KD, except lymphadenopathy, which

Table 2. The relationship between IVIG administration time and coronary artery involvement

		Total	Coronary artery involvement		p-value
			(-)	(+)	
IVIG administration time (day)	n	45	36	9	
	Mean ± SD	7.87±2.89	7.53±2.36	9.22±4.35	[b]0.425
2nd IVIG administration	(-)	37 (82.2)	30 (83.3)	7 (77.8)	[a]0.651
	(+)	8 (17.8)	6 (16.7)	2 (22.2)	
2nd IVIG administration time (day)	n	8	6	2	
	Mean ± SD	9.38±2.13	8.5±1.64	12.00±0.00	-

[a]Fisher's Exact test, [b]Mann-Whitney U test. SD: Standard deviation, IVIG: Intravenous immunoglobulin

Table 3. Risk factors for coronary artery involvement according to Harada scoring system

	Total n (%)	Coronary artery involvement (-) n (%)	Coronary artery involvement (+) n (%)	p-value
Sedimentation (mm/h)				
≤30	0	0	0	-
>30	45 (100)	36 (100)	9 (100)	
CRP (mg/L)				
≤30	2 (4.4)	1 (2.8)	1 (11.1)	[a]0.364
>30	43 (95.6)	35 (97.2)	8 (88.9)	
Albumin (g/dL)				
<3	17 (37.8)	15 (41.7)	2 (22.2)	[a]0.447
≥3	28 (62.2)	21 (58.3)	7 (77.8)	
ALT (IU/L)				
<45	26 (57.8)	21 (58.3)	5 (55.6)	[a]1.000
≥45	19 (42.2)	15 (41.7)	4 (44.4)	
AST (IU/L)				
<45	25 (55.6)	20 (55.6)	5 (55.6)	[a]1.000
>45	20 (44.4)	16 (44.4)	4 (44.4)	
Hemoglobin (g/dL)				
≥10	21 (46.7)	17 (47.2)	4 (44.4)	[a]1.000
<10	24 (53.3)	19 (52.8)	5 (55.6)	
WBC (mm^3)				
≤15,000	17 (37.8)	13 (36.1)	4 (44.4)	[a]0.711
>15,000	28 (62.2)	23 (63.9)	5 (55.6)	
PLT (mm^3)				
<450,000	21 (46.7)	18 (50)	3 (33.3)	[a]0.469
≥450,000	24 (53.3)	18 (50)	6 (66.7)	
Na (mEq/L)				
<133	13 (28.9)	12 (33.3)	1 (11.1)	[a]0.249
≥133	32 (71.1)	24 (66.7)	8 (88.9)	

CRP: C-reactive protein, Na: Sodium, PLT: Platelets, WBC: White blood cells, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, [a]Fisher's Exact test

occurs with a ratio of 40-50% in the literature (1). Gündüz et al. (9) stated oral cavity and lip lesions in 89.7%, conjoctival hyperemia in 76.9%, rash in 74.4%, extremity lesions in 61.5%, and lymphadenopathy in 51.3% of the patients. Our patients had these findings in concordance with the literature with the presence of conjoctival hyperemia and oral mucosal changes mostly and lymphadenopathy less frequently. Perineal desquamation, steril pyuria, and enduration of BCG were some of the additional findings in the patients. According to the studies performed, induration of BCG occurred with a ratio of 16.7%, especially in the incomplete KD (18). Incomplete KD prevelance was 19.8% among the patients with KD in Japan (19). The ratio was between 13.6% and 42% in our country (20,21). Patients with incomplete KD were 24% in our study. The ratios were higher in our country from Japan, suggesting that longlasting fever, which was resistant to antipyretics should remind the KD. Inflammatuary parameters, tended to be higher than normal values, and our results were in accordance with these results.

Cardiovascular involvement is the most threatened complication of this disease. The disease is usually self -limited, but approximately 25-30% of them develop coronary artery involvement. Administering a high dose of IVIG combined with aspirin in the acute phase, especially in the first 7-10 days, is thought to decrease the risk of CAA to 3-5% (22). Different studies established coronary artery lesions with a range of 13-33% (9,23,24), while Gündüz et al. (9) stated the coronary artery involvement with a ratio of 56.4%. Coronary artery involvement may change through a wide range from perivascular echogenity to giant CAAs (9,14). An important coronary artery involvement can result with myocardial infarction and sudden death. Cardiovascular involvement includes the involvement of the pericard, myocard, endocard, and coronary arteries. Findings of heart failure, changes in electrocardiography predicting arrhythmias, angina pectoris, myocardial infarction, cardiomegaly, and pericardial effusion can be present (15). Coronary artery involvement were present in 20% of the patients. None of our patients had electrocardiographic changes reflecting myocardit or pericarditis or ischemia. Cardiomegaly was not detected in our patients. Pericardial effusion was present in one patient. Mitral insufficiency was present in one patient. CALs were present in 9 of the patients, including perivascular echogenity in one, coronary artery dilatation in seven, and moderate Coronary artery involvement in two of them.

Early diagnosis and treatment are critical for managing KD to prevent coronary artery lesions. If the treatment begins after 10 days of the illness, the risk increases. There are some risk factors evaluated for CAAs by different scoring systems (10). The Harada scoring system was introduced in 1991 with high sensitivity (83.3%) to predict coronary artery involvement (25). According to the Harada scoring system, when the parameters mentioned below are present, the risk of coronary artery involvement increases. These parameters are: male sex, age <12 months or >8 years, fever duration >10 days, leukocytosis >15,000/mm^3, low Hgb <10 g/dL, thrombocytosis >450,000/mm^3, hypoalbuminemia (<3 g/dL), hyponatremia, persistent fever, or recurrence of fever >36 h after IVIG administration (2,25). Elevation of inflammatory parameters, including sedimentation, CRP, and WBC, are used to detect systemic inflammation and are used to confirm the diagnosis that are not pathognomonic for KD. Laboratory parameters were evaluated in the patients according to Harada scoring system and the parameters did not show difference in terms of coronary artery involvement. is thought to be related to nonosmotic secretion of antidiuretic hormone and increased vascular permeability. Hyponatremia shows a strong negative correlation with inflammatory mediators such as IL-6 and tumor necrosis factor-alpha (26). Thrombocytosis was related to increased thrombopoietin levels induced by inflammation (27). Hypoalbuminemia is the result of vascular leakage caused by inflammation (28). Sodium, albumin and PLT levels were similar between the patients when they were grouped according to the presence of coronary artery involvement and IVIG resistance.

Öztarhan et al. (10) declared that the frequency of coronary artery lesions (CALs) was 17.6% in their study. There was a male predominance in the patients with CAAs and their age was younger than patients without CALs. Also, the patients <1 years had the highest percentage of CAAs then the other ages. The ratios of complete and incomplete KD was similar in terms of the presence of CAAs. Patients had a frequency of 53.3% in the patients with IVIG resistance. Patients also had higher WBC, PLT, and CRP with similar sedimentation, but lower hematocrit and albumin levels in the presence of coronary involvement (10). Yılmazer et al. (11) stated that patients with IVIG resistance are at a higher risk for coronary artery involvement. Türkuçar et al. (14) exhibited a rate of 33% for CALs, which was similar to Turkish studies but higher than Japanese studies. We showed in our study that gender, age, types of KD, and laboratory parameters did not differ between the patients with coronary involvement and not. Patients <1 years of age and the other age groups had similar ratios of coronary artery involvement. The number of patients >5 years was 9 and only one of them had coronary artery involvement and 2 of them had IVIG

resistance. These results may be related to the limited number of patients included in the study. We also declared in our study that changes in the oral mucosa and lips were less frequently present in the patients with coronary artery involvement. This finding was not declared in the literature earlier. Patients with CALs usually have delayed diagnosis and treatment, so this finding could be healed up or the patient may have incomplete findings supported with additional and laboratory findings at presentation. When we examined in detail, we showed that 5 of the 9 patients with coronary artery involvement had changes in the oral mucosa and lips and 2 of them were incomplete forms of KD.

Although the patients were well treated with IVIG and aspirin, 10-15% of the patients need a second dose of IVIG because of recurrent or persistent fever (1,29). Son et al. (30) declared IVIG resistance with a rate of 13%-21%. When there is IVIG resistance, the administration of the second dose of IVIG is suggested (13). After the second dose of IVIG, fever may be prevalent again in 10%, needing further treatment approaches such as corticosteroids, infliximab, anakinra, cyclosporine, plasma exchange, cyclophosphamide, and rituximab (2,13). Risk factors for IVIG resistance are: age younger than 3 months, incomplete KD, early presence of CAA and early administration of IVIG (≤4 days), delayed administration of IVIG, increased sedimentationand PLT levels. (12,30). Öztarhan et al. (10) stated that IVIG resistance was present with an incidence of 12%. The age at diagnosis under 1 years of age had the highest percentage. IVIG-resistant patients had CAA with a ratio of 50%. WBC, CRP, and ALT were higher, sedimentation and PLT were similar, and hematocrit, and Na were lower in the IVIG-resistant group (10). Yılmazer et al. (11) showed in his study the presence of lower albumin but higher CRP and WBC in the IVIG-resistant group. Ashouri et al. (29) also exhibited low albumin and low sodium levels in their study. Also, it is known that the incomplete form is more likely to be IVIG resistant (11). Li et al. (31) and Egami et al. (32) speculated that not only increased PLT levels but also decreased PLT values are risk factors for IVIG resistance because of intravascular consumption, reflecting greater inflammation. Kobayashi et al. (33) suggested that the presence of PLT ≤300,000 mm^3 was a predictor for IVIG resistance. Our patients with IVIG resistance consisted of 17% of the patients. Age distribution, type of KD, and laboratory findings were similar between the IVIG-resistant and IVIG-responsive groups caused by the probabl effect of a limited number of the patients included. Yılmazer et al. (11) declared similar incidences of principal findings in the IVIG responders and non-responder group. Principal findings were similar between the groups in our study like the study by Yılmazer et al. (11). Desquamation of perine is more prevalent in the IVIG-resistant group in our study. There is not a study performed in the literature evaluating additional findings in terms of IVIG resistance. Perineal desquamation is more prevalent at the end of the subacute phase, and these patients are usually not diagnosed until this time who are more likely to have an incomplete form of KD (2,9). Incomplete KD is more related with IVIG resistance according to the studies in the literature (9,11,13). All the patients with perineal desquamation who had IVIG resistance were incomplete form of KD in our study, compatible with the literature.

It is known that there is a relationship with administration time of IVIG and coronary artery involvement. Türkuçar et al. (14) declared that, longer duration of fever and delayed administration of IVIG accompanied with higher CRP were risk factors for IVIG resistance. Also, it is important to treat these patients in the first 7-10 days to prevent CALs. When we evaluate our patients according to this knowledge, we can state that the administration time of the first IVIG did not differ between the groups in terms of coronary artery involvement and it is under 10 days in both of them. Nearly 17% of our patients had IVIG resistance compatible with the literature, and 25% of the patients with IVIG resistance had coronary artery involvement. The administration time of the second IVIG was after 10 days in the group with coronary artery involvement in our study.

All the patients were treated with IVIG and aspirin at anti-inflammatory dosage as it is suggested in the literature. Aspirin treatment is administered with a dose of 30-50 mg/kg/dose (moderate dose) in Japan and 80-100 mg/kg/dose (high dose) in the USA. The difference in dosage is related to the difference in sensitivity to aspirin. There is no clear evidence that any dose of ASA will decrease the development of CAAs. Therefore moderate dose is preferred because of the potential toxicities (2,7). Aspirin dosage was reduced to 3-5 mg/kg/dose after fever was resolved (7). Some clinicians continued anti-inflammatory dose until 14th day of illness (2). IVIG -resistant patients were treated with a second dose of IVIG. Repeated IVIG resistance was usually treated with pulse methylprednisolone (11,12). Lu et al. (13) administered pulse methylprednisolone followed by oral prednisone tapered in one week. We used aspirin with a dose of 80-100 mg/kg, and after fever resolves aspirin dosage was reduced to antiaggregan dose. Repeated IVIG resistance was treated with pulse methylprednisolone in 2 patients in our study.

Patients without CAA were treated with aspirin of 3-5 mg/kg/dose for 6-8 weeks. Patients with moderate-sized CAAs

were treated with aspirin and clopidogrel. Giant CAAs are treated with antiplatelet and anticoagulant agents such as low-molecule weight heparin and warfarin (2,7). CAAs with grade 0 include coronary arteries that do not have the effect of the disease. Grade 1 includes CAAs, which usually show natural regression within 1 year. Grade 2 includes medium-sized CAAs, which show regression within 2 years in more than half of the cases. Grade 3 includes CAAs that may develop stenosis or occlusion in the future even though high-dose anticoagulant and antiaggregan therapy is administered (3). There was not a patient with giant CAA in our study. There were two patients with moderate CAAs who were treated with aspirin and clopidogrel. The other 7 patients with CALs with perivascular echogenity and mild dilatation were treated only with aspirin for two months. Only one of the moderate CAAs persisted for 1 year. The other one does not keep coming to follow-ups, so we do not have the knowledge about the other CAA.

CONCLUSION

KD should be considered in the differential diagnosis of longlasting fever, which cannot be explained with other reasons in children under 5 years of age. Principal findings combined with additional and laboratory findings should be used for diagnose. Changes in the oral mucosa and lips are less frequent in the patients with coronary artery involvement, whereas perineal desquamation is more prevalent among the patients with IVIG resistance. These findings were not been mentioned in the literature previously. Laboratory findings were not predictive for coronary artery involvement and IVIG resistance in our study. All of our patients were treated properly, and there has not been a cardiac sequel during follow-ups. As a result, even though KD can result with severe complications, timely and correct diagnosis and treatment of the disease usually guarantees a good prognosis.

ETHICS

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2022-20-08, date: 17.10.2022) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from the patients and their parents.

Authorship Contributions

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

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Research

Bronchial Artery Embolization Treatment During COVID-19 Pandemic: A Single-center Experience

COVİD-19 Pandemisi Sırasında Bronşiyal Arter Embolizasyon Tedavisi: Tek Merkez Deneyimi

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ABSTRACT

Objective: Bronchial artery embolization (BAE) now serves as the standard treatment for hemoptysis. The aim of this study was to determine the characteristics and outcomes of the patients who undergo BAE during the coronavirus disease-2019 pandemic period.

Methods: We retrospectively investigated patients that presented to the hospital with hemoptysis and received bronchial arterial embolization treatment during the pandemic period. Age, gender, history of previous diseases, and related data were collected.

Results: The study was conducted with 11 patients whose 18.18% (n=2) were female and 81.81% (n=9) were male. The mean age of the patients is 61.27±10.94 and they stayed in hospital 21.18±19.59 days on average. Infection and bronchiectasis were seen as the leading cause of hemorhagee. Also, alveolar hemorrhage seen 81.8% (n=9) of the patients. Dilated bronchial arteries were seen on 72.7% (n=8) of the patients. Although 54.5% (n=6) of the patients admitted to the intensive care unit after the procedure, no complication or mortality seen in any patient during the procedure.

Conclusion: Bronchial arterial embolization is an effective minimally invasive technique for treating hemoptysis. This invasive procedure could be applied safely during the pandemic period.

Keywords: Bronchial artery embolization, hemoptysis, COVID-19

ÖZ

Amaç: Bronşiyal arter embolizasyonu (BAE) artık hemoptizi için standart tedavi olarak kullanılmaktadır. Bu çalışmanın amacı, koronavirüs hastalığı-2019 pandemisi döneminde BAE uygulanan hastaların özelliklerini ve sonuçlarını tespit etmektir.

Gereç ve Yöntem: Pandemi döneminde hemoptizi ile hastaneye başvuran ve BAE tedavisi alan hastaları retrospektif olarak incelendi. Yaş, cinsiyet, geçirilmiş hastalık öyküsü ve ilgili verileri toplandı.

Bulgular: Çalışma %18,18 (n=2) kadın, %81,81 (n=9) erkek olan 11 hasta ile gerçekleştirildi. Hastaların yaş ortalaması 61,27±10,94 olup, ortalama 21,18±19,59 gün hastanede yatış süresi vardı. Enfeksiyon ve bronşektazi kanamanın önde gelen nedeni olarak görüldü. Ayrıca hastaların %81,8'inde (n=9) alveoler hemoraji görüldü. Hastaların %72,7'sinde (n=8) genişlemiş bronşiyal arterler görüldü. İşlem sonrası yoğun bakıma yatırılan hastaların %54,5'inde (n=6), işlem sırasında ise hiçbir hastada komplikasyon veya mortalite görülmedi.

Sonuç: BAE hemoptizi tedavisinde etkili minimal invaziv bir tekniktir. Bu invaziv prosedür pandemi döneminde güvenle uygulanabilir.

Anahtar Kelimeler: Bronşiyal arter embolizasyonu, hemoptizi, COVİD-19

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INTRODUCTION

Hemoptysis is the expectoration of bleeding originating from the tracheobronchial tree or lung parenchyma (1). The annual frequency of the diagnosis of hemoptysis is 10% in patients with chronic lung disease, with an incidence in any outpatient being reported as approximately 0.1% (1,2). Although more than 90% of hemoptysis cases are self-limiting, it is still a potentially life-threatening emergency (3). The manifestation of hemoptysis can vary from streaks of blood in the phlegm to massive bleeding that can be fatal. Therefore, hemoptysis requires a rapid diagnosis and treatment, but it is difficult to diagnose (4). Massive hemoptysis is defined as 200 mL or more blood expectoration at a time or more than 500 mL blood in 24 h (5). Of the blood supply to the lungs, 99% is provided by the pulmonary arteries, which are responsible for gas exchange, and the remaining 1% by the bronchial arteries.

Considering the causes of hemoptysis, half of the cases are due to unknown bleeding, but inflammatory lung diseases (25%), bronchial carcinoma and metastases (17%), bronchiectasis (7%), and less frequently cardiovascular diseases and anticoagulant use can also be effective factors (6). Bronchial artery angiography with bronchial artery embolization (BAE) is a minimal invasive technique that has emerged as a standard treatment for hemoptysis (7). It involves selective bronchial artery catheterization and angiography, followed by embolization of any aberrant blood vessels discovered to stop the bleeding. Patients with large and recurring hemoptysis have been treated with BAE (8). However, rebleeding can occur even after an apparently successful BAE (9,10).

Coronavirus disease-2019 (COVID-19) is caused by a new coronavirus known as severe acute respiratory syndrome coronavirus-2. The first case emerged in Wuhan, China in -November 2019, and the disease rapidly spread across the world. The most widely used method for the diagnosis of the disease is real-time reverse-transcriptase polymerase chain reaction test on a nasopharyngeal swab. Common symptoms include headache, loss of smell and taste, nasal congestion and runny nose, cough, muscle pain, sore throat, fever, and difficulty in breathing. There are only a few case reports detailing the BAE experience during the COVID-19 pandemic in the existing literature (11,12).

In this study, we retrospectively evaluated the relationship between COVID-19 infection, which causes lung infections, and hemoptysis that we treated with BAE.

METHODS

This study involved a retrospective analysis of 11 patients, two female and nine male, aged 39-80 years, who underwent bronchial arterial embolization at the University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital from June 2020, through June 2021. The University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Instutional Review Board approved the study (decision no: 2022/514/238/9, date: 29/11/2022). All procedures involving human participants were approved in accordance with the ethical standards of the Institutional and/or National Research Committee, including the Helsinki Declaration of 1964 and its subsequent amendments or comparable ethical standards. Age, gender, previous disease history, and related data were collected from all patients. All patients who underwent the BAE procedure during the COVID-19 period were included in the study. Informed consent was obtained from all the patients before the procedure.

The sample consisted of cases that presented to the emergency department with the complaint of hemoptysis, in which upper airway bleeding was excluded by performing otolaryngology consultations following routine hemodynamic monitoring and laboratory tests. Routine cardiology consultations were made, and cardiac causes were also excluded. The follow-up of the patients was continued in the chest diseases department, and thoracic computed tomography and fiberoptic bronchoscopy procedures were also undertaken in the patients. Two patients required emergency BAE, whereas the rest patients underwent elective BAE. The patients were transferred to the interventional radiology unit, and the BAE procedures were performed. Patients' demographic information, vital signs (blood pressure, body temperature, pulsu, oxygen saturation), and blood parameters (hemoglobin, hematocrit, platelet count, and international normalized ratio) were included in the study's data form. Additionally, the hospital automation system was used to record the amount of hemoptysis, the number of embolized bronchial arteries, the length of hospital stay, the usage of anticoagulants, and the prevalence of chronic disease.

Statistical Analysis

The SPSS 25.0 package program was used for statistical analysis of the data. Categorical measures as numbers and percentages, and mean and standard deviation for continuous measurements (required summarized as median and minimum-maximum).

RESULTS

A total 11 patients were included to study. The patients 18.18% (n=2) were female and 81.81% (n=9) were male. The mean age of the patients was 61.27 years, and the mean length of hospital stay was approximately 21 days.

Tables 1 and 2 present the mean, standard deviation, minimum, and maximum values of continuous variables and the frequencies and percentages of discrete variables, respectively. In the duration of our research, the participants' blood pressure, pulse rates, and oxygen saturations were never measured to be lower than the standard ranges. Simultaneously, it was discovered that the patients' entrance hemoglobin and hematocrit values were not significantly below the baseline. All the patients who participated in the study were found to have a history of smoking. As can be seen in Table 1, neither thrombocytopenia nor an international normalized rate prolongation, which may be the cause of bleeding, were seen in any patient. In every patient, at least one and no more than two of the bronchial arteries were blocked with embolic material.

Alveolar bleeding occurred in 81.8% of patients, and dilated bronchial arteries occurred in 72.7% of patients. These were the two most prevalent findings (Table 2). Only two of the patients in our study had bronchiectasis, which is a significant contributor to the development of hemoptysis. However, nine of the patients did not have this condition. No complication occurred in any patient during the procedure, and general anesthesia was not applied to any patient.

DISCUSSION

BAE was first described in 1973 by Remy et al. (13) and is still a popular technique with its success for treating hemoptysis.

The most common symptoms of COVID-19, which emerged in 2019 and continues to affect the worldwide, include fever, dry cough, shortness of breath, widespread muscle aches, fatigue, and loss of taste and smell (14-16). Additionally, specific clinical results have also emerged, with the most prominent examples being vascular bed disorders. In addition to causing emboli-like diseases, such as stroke and myocardial infarction, COVID-19 can result in bleeding without disturbing the vascular structure (17).

In an autopsy study of seven patients that died due to COVID-19, it was reported not only vasculitis and microthrombus involving all the vessel segments but also severe endothelial damage and pathological angiogenesis on lung microangiopathy (18).

Although hemoptysis is a rare finding in patients with COVID-19, studies have shown that it may also be the first sign (16,19). In a cohort study, it was reported the coexistence of COVID-19 and hemoptysis at a rate of 0.9%, and that of severe COVID-19 cases and hemoptysis at 2.3% (20). In another cohort study, 3% of the patients were found

Table 1. Basic statistics of continuous variables

Variables	n	Mean	Minimum	Maximum	Standard deviation
Age (year)	11	61.27	39.00	80.00	10.94
SAP (mmHg)	11	108.82	96.00	126.00	8.94
DAP (mmHg)	11	67.09	55.00	90.00	10.34
Body temperature (°C)	11	36.37	36.00	36.90	0.36
Pulse (/dk)	11	84.00	65.00	110.00	13.71
SpO_2 (%)	11	95.00	88.00	98.00	3.46
Hemoglobulin (g/dL)	11	12.40	9.00	17.00	2.42
Hematocrit (%)	11	35.80	29.10	44.70	4.65
Platelet count (per/mL)	11	251.36	161.00	472.00	103.67
INR	11	1.12	0.91	1.47	0.18
Smoking (number of packs per year)	11	26.09	0.00	50.00	20.94
EF (%)	11	57.22	50.00	65.00	5.07
Hemoptysis quantity	11	277.27	150.00	350.00	68.42
Number of bronchial arteries embolized	11	1.36	1.00	2.00	0.50
Length of stay in hospital (days)	11	21.18	5.00	53.00	19.59

SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, INR: International normalized rate, EF: Ejection fraction SpO_2: Peripheral oxygen saturation

to have COVID-19 and hemoptysis (21). In our study, two of the 11 patients that underwent BAE due to hemoptysis had a history of bronchiectasis and six had a history of malignancy.

Table 2. Frequency and percentages of discrete variables

Variables	Group	Frequency	Percentage
Anticoagulant use	Absent	6	54.5
	Present	5	45.5
Bronchiectasis	Absent	9	81.8
	Present	2	18.2
Infection	Absent	7	63.6
	Present	4	36.4
Tuberculosis	Absent	10	90.9
	Present	1	9.1
Others	Absent	5	45.5
	Present	6	54.5
Alveolar hemorrhage	Absent	2	18.2
	Present	9	81.8
Condensation	Absent	6	54.5
	Present	5	45.5
Dilated bronchial arteries	Absent	3	27.3
	Present	8	72.7
Pulmonary artery lesion	Absent	11	100.0
Emergency intervention	Absent	8	72.7
	Present	3	27.3
Complication during procedure	Absent	11	100.0
Malignancy	Absent	6	54.5
Complication during procedure	Present	5	45.5
Coronary heart disease	Absent	5	45.5
	Present	6	54.5
Hypertension	Absent	6	54.5
	Present	5	45.5
Chronic renal insufficiency	Absent	10	90.9
	Present	1	9.1
Pulmonary shunt	Absent	6	54.5
	Present	5	45.5
Mortality	Absent	11	100.0
ICU admission	Absent	5	45.5
	Present	6	54.5

ICU: Intensive care unit

In a study from China evaluating 1,099 patients, it was reported that 56% of the patients had a radiological ground-glass appearance, but no radiological finding was present in 18% of the cases (20). The imaging features of COVID-19 are similar to those of alveolar hemorrhage, and therefore they can be misinterpreted. As a result, thoracic tomography may not be sufficient to determine the location of the bleeding.

Although BAE emerged as a treatment option for dilated bronchial artery structures, it also started to be used for treating advanced hemoptysis cases without non-dilated bronchial arteries or structural problems in the lung during the COVID-19 pandemic. Many studies have shown that BAE is a safe and effective treatment option in cases of emergency and/or recurrent hemoptysis (22-24). This is also supported by our findings.

Even though BAE is a complex interventional procedure, the success it has produced in therapy should be more widely incorporated into medical practice because it has saved lives. Endovascular treatment alternatives should be administered by more physicians and in more facilities. To lower mortality rates during a pandemic and to arrange the treatment of non-pandemic emergencies, such advanced interventional therapy procedures should continue to be made available. This study also shown these good outcomes.

CONCLUSION

In conclusion, we consider that BAE is an effective treatment in cases of hemoptysis, which is frequently encountered during the COVID-19 pandemic.

ETHICS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (decision no: 2022/514/238/9, date: 29/11/2022).

Informed Consent: Written informed consent was taken from all patients due to nature of procedure.

Authorship Contributions

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

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

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19. Argun Barış S, Coşkun İS, Selvi G, Boyacı H, Başyiğit İ. Case Series of COVID-19 Presenting with Massive Hemoptysis. Turk Thorac J 2020;21:454-6.
20. 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.
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Research

Meningioma: A Bibliometric Analysis of the 50 Most Cited Articles

Menenjiyom: En Çok Atıf Alan 50 Makalenin Bibliyometrik Analizi

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ABSTRACT

Objective: It was aimed to contributing to contributing to the literature by making a bibliometric analysis of original scientific research on meningiomas.

Methods: We reviewed the literature using Thomson-Reuters Web of Science-Science Citation Index Expanded database. The 50 most cited articles containing the keyword meningioma were identified. The number of citations, the country and institute of submission, the name of the publishing journal, the year of publication, and the content of the articles were noted. The top-publishing journals were searched using the multidisciplinary database Scopus, through the free-access portal SCImago Country & Journal Rank (SJR). The documents they published, the citations they received, and the citation/document ratios for the last two years were collected.

Results: When the 50 most cited articles were examined, it was seen that they recorded a total of 17,432 and an average of 348.6 citations. While the most cited article received 1237 citations, the least cited one was cited 196 times. The most common field of study in these articles (22%) was a cytogenetic study. Other article types and topics were radiosurgery, classification score system, progression, epidemiology-etiology, review, surgical outcomes, and radiology. More than half (54%) of the articles consisted of the studies conducted in the US. Germany followed this country with 14%. These studies were conducted at 36 different institutes. The institute that conducted the highest number of studies is the Mayo Clinic. These articles have been published in 25 different journals. Eight journals published at least 2 articles. The Journal of Neurosurgery, which published 20% of the articles, outnumbered other journals. It is followed by the International Journal of Radiation Oncology Biology Physics and the Journal of Neurosurgery with five articles each. We identified 8 journals which published 2 or more of the 50 most cited articles on meningioma. Examining these journals using the data obtained from SJR, with Scopus data, we have seen that the average number of citations per document (cites/doc.) was 4.14, the average total documents were 949.7 in 2020, and the average total number of citations for those documents was 18307.1.

Conclusion: The findings of this study show that an article about meningioma is more likely to be cited highly if it was published in a subject-specific journal of an English-speaking institution in the US.

Keywords: Meningioma, bibliometric, analysis

ÖZ

Amaç: Çalışmamızda, menenjiyomlarla ilgili yayınlanmış özgün bilimsel araştırmaların bibliyometrik analizini yapmayı ve literatüre katkı sağlamayı amaçladık.

Gereç ve Yöntem: Literatür taraması Thomson Reuters Web of Science-Science Citation Index Expanded veri tabanı kullanılarak yapılmıştır. Meningioma anahtar kelimelerini içeren en çok atıf alan 50 makale tespit edildi. Makalelerin atıf sayısı, gönderildiği ülke ve enstitü, yayınlayan dergi, yayın yılı ve makalenin içeriği kayıt altına alındı. En çok yayın yapan dergiler multidisciplinary database Scopus, through the free-access portal SCImago Country & Journal Rank (SJR) kullanılarak tarandı ve yayınladıkları dokümanlar, aldıkları atıflar ve son iki yıllık atıf/doküman oranları toplandı.

Bulgular: En fazla atıf alan 50 makale incelendiğinde, en az atıf alan makalenin 196 ve en çok atıf alan makalenin 1237 atıf aldığı ve toplamda 17.432 ve ortalama 348,6 atıf aldığı görüldü. En sık makale türü (%22) sitogenetik çalışmalardı. Diğerleri radyocerrahi, sınıflandırma skor sistemi, progresyon, epidemiyoloji-etiyoloji, derleme, cerrahi sonuçlar ve radyoloji idi. Makalelerin yarıdan fazlası (%54) ABD'de yürütülmüş çalışmalardı. ABD'yi %14 ile Almanya takip ediyordu. Bu çalışmalar 36 farklı enstitüde yapılmış olup 5 araştırma ile en çok çalışma yapan enstitü Mayo Clinic idi. Makaleler 25 farklı dergide yayınlanmıştır. Sekiz dergide 2 ve 2'den çok makale yayınlanmıştır. En çok makale (%20) Journal of Neurosurgery'de

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ÖZ

yayınlanmıştır. Journal of Neurosurgery'i beşer makale ile International Journal of Radiation Oncology Biology Physics ve Neurosurgery dergileri takip etmektedir. SJR ile Scopus data ulaşılan verilerde en çok atıf alan menenjiyom çalışmalarının 2 ve daha fazla sayıda yayın yapan sekiz derginin doküman başına yapılan atıf sayısı (cites/doc.) ortalama 4,14, ortalama toplam dokümanları 2020 yılı içinde 949,7 ve bu dökümanlar için yapılan ortalama toplam atıf sayıları 18307,1 olarak saptanmıştır.

Sonuç: Menenjiyom hakkında bir makalenin yüksek oranda atıf alması için ABD'de İngilizce konuşulan bir kurumdan konuya özel bir dergide yayınlanmasının daha olası olduğu görülmektedir.

Anahtar Kelimeler: Menenjiyom, bibliyometrik, analiz

INTRODUCTION

Meningiomas are the most common (36.6%) primary intracranial tumors (1). The incidence of meningioma depends on age; while it occurs in 0.14 per 100,000 children aged 0-19, it is 37.75 per 100,000 in the 75-84 age group (1-2). They originate from arachnoidal cap cells and often adhere to the dura (3). They are mostly benign tumors, but there are also variants with malign features (4). The diagnosis of meningiomas has increased significantly with cross-sectional imaging techniques such as magnetic resonance imaging and multi-detector computed tomography (5).

In parallel with the overall increase in the number of publications recently, the number and variety of bibliometric studies have also increased (6). With many bibliometric studies conducted in this field, thousands or even tens of thousands of studies have been analyzed, thus creating a valuable source for new research. Bibliometric analysis reveals actively publishing authors, institutes, countries, journals, and their relations with each other (6). Examining the most cited publications is a frequently used method in bibliometric analysis (7,8). The number of citations of an article is an important objective indicator showing the extent of credit and interest it gets in the academic world (9). For this reason, in bibliometric studies, the 50 most cited publications are filtered and analyzed (7).

A review of the literature shows that many bibliometric studies have been conducted on various subjects in the field of neurosurgery (6,10-14). We also planned to review the 50 most cited publications on meningioma using the Thomson ISI Web of Science® Database.

METHODS

In March 2022, we searched the term "meningioma" in the "title" section and in Neurology and Neuroscience categories of the Thomson Reuters Web of Science-Science Citation Index Expanded database. The 50 most cited articles published in English since 1970 were examined.

The parameters we noted were the number of citations, the country and institute where they were submitted, the publishing journal, the year of publication, and the content of the articles. Eight journals that published two or more articles were searched using the multidisciplinary database Scopus, through the free-access portal SCImago Country & Journal Rank (SJR). The documents published by these eight journals, the citations they received, and the citation/document ratios for the last two years were noted.

The period from 1970 to present was divided into decades and grouped by the year articles were published. The content of the articles was categorized as cytogenetic studies, non-surgical or radiosurgery studies, studies on classification and scoring, progression, epidemiology-etiology studies, reviews, surgical outcome studies, and radiological studies.

Statistical Analysis

The IBM SPSS Statistics Co. 25.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis. Qualitative data were defined as frequency distributions and quantitative data were presented as mean, minimum, and maximum values.

RESULTS

When the 50 most cited articles were examined, it was seen that they recorded a total of 17,432 and an average of 348.6 citations. While the most cited article received 1237 citations, the least cited one was cited 196 times (Table 1). The articles were found to be under eight different research titles. The most common article field was cytogenetic studies with 11 articles (Table 2). Others were radiosurgery, classification score system, progression, epidemiology-etiology, review, surgical outcomes, and radiology.

More than half (54%) of the articles were on studies conducted in the US, followed by Germany with 14%. The studies that led to the publication of 50 articles were conducted at 36 different institutes from 12 different countries (Figure 1). The institute that carried out the highest number of studies (5) is the Mayo Clinic (Table 3).

Table 1. The 50 most cited articles on meningioma

No	Article	Number of citations
1	Marosi C, Hassler M, Roessler K, Reni M, Sant M, Mazza E, et al. Meningioma. Crit Rev Oncol Hematol 2008;67:153-71.	394
2	Abdel-Rahman MH, Pilarski R, Cebulla CM, Massengill JB, Christopher BN, Boru G, et al. Germline BAP1 mutation predisposes to uveal melanoma, lung adenocarcinoma, meningioma, and other cancers. J Med Genet 2011;48:856-9.	430
3	Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. J Neurooncol 2010;99:307-14.	1010
4	Rohringer M, Sutherland GR, Louw DF, Sima AA. Incidence and clinicopathological features of meningioma. J Neurosurg 1989;71:665-72.	493
5	Kalamarides M, Niwa-Kawakita M, Leblois H, Abramowski V, Perricaudet M, Janin A, et al. *Nf2* gene inactivation in arachnoidal cells is rate-limiting for meningioma development in the mouse. Genes Dev 2002;16:1060-5.	212
6	Claus EB, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M, Black PM. Epidemiology of intracranial meningioma. Neurosurgery 2005;57:1088-95.	618
7	Commins DL, Atkinson RD, Burnett ME. Review of meningioma histopathology. Neurosurg Focus 2007;23:E3.	205
8	Kollova A, Liščák R, Novotný J, Vladyka V, Šimonová G, Janoušková L. Gamma Knife surgery for benign meningioma. J Neurosurg 2007;107:325-36.	209
9	Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM. Meningioma grading: an analysis of histologic parameters. Am J Surg Pathol 1997;21:1455-65.	719
10	Buetow MP, Buetow PC, Smirniotopoulos JG. Typical, atypical, and misleading features in meningioma. Radiographics 1991;11:1087-106.	375
11	Levy WJ, Bay J, Dohn D. Spinal cord meningioma. J Neurosurg 1982;57:804-12.	426
12	Clark VE, Erson-Omay EZ, Serin A, Yin J, Cotney J, Özduman K, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science 2013;339:1077-80.	627
13	Jääskeläinen J. Seemingly complete removal of histologically benign intracranial meningioma: late recurrence rate and factors predicting recurrence in 657 patients. A multivariate analysis. Surg Neurol 1986;26:461-9.	538
14	Lamszus K. Meningioma pathology, genetics, and biology. J Neuropathol Exp Neurol 2004;63:275-86.	238
15	Weber RG, Boström J, Wolter M, Baudis M, Collins VP, Reifenberger G, et al. Analysis of genomic alterations in benign, atypical, and anaplastic meningiomas: toward a genetic model of meningioma progression. Proc Natl Acad Sci U S A 1997;94:14719-24.	433
16	Longstreth Jr WT, Dennis LK, McGuire VM, Drangsholt MT, Koepsell TD. Epidemiology of intracranial meningioma. Cancer 1993;72:639-48.	386
17	Nauta HJ, Tucker WS, Horsey WJ, Bilbao JM, Gonsalves C. Xanthochromic cysts associated with meningioma. J Neurol Neurosurg Psychiatry 1979;42:529-35.	218
18	McCarthy BJ, Davis FG, Freels S, Surawicz TS, Damek DM, Grutsch J, et al. Factors associated with survival in patients with meningioma. J Neurosurg 1998;88:831-9.	238
19	Milker-Zabel S, Zabel A, Schulz-Ertner D, Schlegel W, Wannenmacher M, Debus J. Fractionated stereotactic radiotherapy in patients with benign or atypical intracranial meningioma: long-term experience and prognostic factors. Int J Radiat Oncol Biol Phys 2005;61:809-16.	204
20	Pasquier D, Bijmolt S, Veninga T, Rezvoy N, Villa S, Krengli M, et al. Atypical and malignant meningioma: outcome and prognostic factors in 119 irradiated patients. A multicenter, retrospective study of the Rare Cancer Network. Int J Radiat Oncol Biol Phys 2008;71:1388-93.	196
21	Taylor Jr BW, Marcus Jr RB, Friedman WA, Ballinger Jr WE, Million RR. The meningioma controversy: postoperative radiation therapy. Int J Radiat Oncol Biol Phys 1988;15:299-304.	334
22	Zorludemir S, Scheithauer BW, Hirose T, Van Houten C, Miller G, Meyer FB. Clear cell meningioma. A clinicopathologic study of a potentially aggressive variant of meningioma. Am J Surg Pathol 1995;19:493-505.	260
23	Sadetzki S, Flint-Richter P, Ben-Tal T, Nass D. Radiation-induced meningioma: a descriptive study of 253 cases. J Neurosurg 2002;97:1078-82.	257
24	Goyal LK, Suh JH, Mohan DS, Prayson RA, Lee J, Barnett GH. Local control and overall survival in atypical meningioma: a retrospective study. Int J Radiat Oncol Biol Phys 2000;46:57-61.	245

25	Mirimanoff RO, Dosoretz DE, Linggood RM, Ojemann RG, Martuza RL. Meningioma: analysis of recurrence and progression following neurosurgical resection. J Neurosurg 1985;62:18-24.	1237
26	Willis J, Smith C, Ironside JW, Erridge S, Whittle IR, Everington D. The accuracy of meningioma grading: a 10-year retrospective audit. Neuropathol Appl Neurobiol 2005;31:141-9.	228
27	Carella RJ, Ransohoff J, Newall J. Role of radiation therapy in the management of meningioma. Neurosurgery 1982;10:332-9.	264
28	Seizinger BR, De La Monte S, Atkins L, Gusella JF, Martuza RL. Molecular genetic approach to human meningioma: loss of genes on chromosome 22. Proc Natl Acad Sci U S A 1987;84:5419-23.	371
29	Zang KD. Cytological and cytogenetical studies on human meningioma. Cancer Genet Cytogenet 1982;6:249-74.	328
30	Couce ME, Aker FV, Scheithauer BW. Chordoid meningioma: a clinicopathologic study of 42 cases. Am J Surg Pathol 2000;24:899-905.	216
31	van Alkemade H, de Leau M, Dieleman EM, Kardaun JW, van Os R, Vandertop WP, et al. Impaired survival and long-term neurological problems in benign meningioma. Neuro Oncol 2012;14:658-66.	209
32	Claus EB, Calvocoressi L, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M. Dental x-rays and risk of meningioma. Cancer 2012;118:4530-7.	228
33	Dziuk TW, Woo S, Butler EB, Thornby J, Grossman R, Dennis WS, et al. Malignant meningioma: an indication for initial aggressive surgery and adjuvant radiotherapy. J Neurooncol 1998;37:177-88.	300
34	Milosevic MF, Frost PJ, Laperriere NJ, Wong CS, Simpson WJ. Radiotherapy for atypical or malignant intracranial meningioma. Int J Radiat Oncol Biol Phys 1996;34:817-22.	242
35	Al-Mefty O, Kadri PA, Pravdenkova S, Sawyer JR, Stangeby C, Husain M. Malignant progression in meningioma: documentation of a series and analysis of cytogenetic findings. J Neurosurg 2004;101:210-8.	238
36	Sahm F, Schrimpf D, Stichel D, Jones DT, Hielscher T, Schefzyk S, et al. DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Lancet Oncol 2017;18:682-94.	424
37	George B, Lot G, Boissonnet H. Meningioma of the foramen magnum: a series of 40 cases. Surg Neurol 1997;47:371-9.	226
38	Stafford SL, Pollock BE, Foote RL, Link MJ, Gorman DA, Schomberg PJ, et al. Meningioma radiosurgery: tumor control, outcomes, and complications among 190 consecutive patients. Neurosurgery 2001;49:1029-38.	415
39	Sahm F, Schrimpf D, Olar A, Koelsche C, Reuss D, Bissel J, et al. TERT promoter mutations and risk of recurrence in meningioma. J Natl Cancer Inst 2015;108:djv377.	233
40	Kondziolka D, Levy EI, Niranjan A, Flickinger JC, Lunsford LD. Long-term outcomes after meningioma radiosurgery: physician and patient perspectives. J Neurosurg 1999;91:44-50.	348
41	Goel A, Muzumdar D, Desai KI. Tuberculum sellae meningioma: a report on management on the basis of a surgical experience with 70 patients. Neurosurgery 2002;51:1358-64.	245
42	Perry A, Scheithauer BW, Stafford SL, Abell-Aleff PC, Meyer FB. "Rhabdoid" meningioma: an aggressive variant. Am J Surg Pathol 1998;22:1482-90.	253
43	Flickinger JC, Kondziolka D, Maitz AH, Lunsford LD. Gamma knife radiosurgery of imaging-diagnosed intracranial meningioma. Int J Radiat Oncol Biol Phys 2003;56:801-6.	234
44	Schüz J, Böhler E, Berg G, Schlehofer B, Hettinger I, Schlaefer K, et al. Cellular phones, cordless phones, and the risks of glioma and meningioma (Interphone Study Group, Germany). Am J Epidemiol 2006;163:512-20.	311
45	Maier H, Öfner D, Hittmair A, Kitz K, Budka H. Classic, atypical, and anaplastic meningioma: three histopathological subtypes of clinical relevance. J Neurosurg 1992;77:616-23.	355
46	Ayerbe J, Lobato RD, De la Cruz J, Alday R, Rivas JJ, Gómez PA, et al. Risk factors predicting recurrence in patients operated on for intracranial meningioma. A multivariate analysis. Acta Neurochir (Wien) 1999;141:921-32.	210
47	Heuser M, Beutel G, Krauter J, Döhner K, von Neuhoff N, Schlegelberger B, et al. High meningioma 1 (MN1) expression as a predictor for poor outcome in acute myeloid leukemia with normal cytogenetics. Blood 2006;108:3898-905.	271
48	Al-Mefty O. Clinoidal meningiomas. J Neurosurg 1990;73:840-9.	277
49	Benson VS, Pirie K, Green J, Casabonne D, Beral V. Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort. Br J Cancer 2008;99:185-90.	209
50	Pieper DR, Al-Mefty O, Hanada Y, Buechner D. Hyperostosis associated with meningioma of the cranial base: secondary changes or tumor invasion. Neurosurgery 1999;44:742-6.	295

These articles have been published in 25 different journals. 8 journals published at least 2 or more articles (Table 4). The highest number of articles (10) was published by the Journal of Neurosurgery, which is followed by the International Journal of Radiation Oncology, Biology Physics, and the Journal of Neurosurgery with 5 articles each. We identified 8 journals which published 2 or more of the 50 most cited articles on meningioma. Examining the 8 journals using the data obtained from SJR, with Scopus data, we have seen that the average number of citations per document (cites/doc.) was 4.14, the average total documents were 949.7 in 2020, and the average total number of citations for those documents was 18307.1.

DISCUSSION

We have listed 50 most-cited articles on meningiomas. We found that these articles were published on studies conducted in 12 different countries, while the US accounted for more than half (54%) of them (Figure 1). This result is in line with the findings of other bibliometric studies (6,10-14). It goes without saying that economic development lays a suitable ground for advances in science and technology (15). The US's ability to allocate funding and resources for scientific research thanks to its economic power enabled this country to outperform in this field, which can also be observed in the findings of this study. Based on our observation, it appears that an article on meningiomas is more likely to be cited highly if it was published in a subject-specific journal (Neurosurgery or Radiation oncology) by an English-speaking institution in the US. It is also not a coincidence that the five leading countries in terms of scientific publications are the US, Germany, Canada, France, and the UK, respectively, which enjoy developed economies and scientific productivity. In this vein, this study suggests that there is a linear relationship between the number of publications on meningiomas in these countries and their economic power. This situation gives important information about the influence of developed countries in conducting scientific studies.

When the article types were examined, the cytogenetic studies outnumbered articles in other fields. The World Health Organization (WHO) published its central nervous system classification in 1979, 1993, 2000, 2007, 2016, and 2020 (16). The importance of histomorphological features and molecular changes has increased in the last two updates. In this way, the WHO reduced the interobserver variability of histological interpretation in diagnostic criteria and to provide a more accurate classification of clinical outcomes. In accordance with this, cytogenetic studies have been widely cited and received interest in studies on meningiomas (Table 2).

Table 2. Frequent article contents

Article content	n
Cytogenetic	11
Non-surgical (radiosurgery)	10
Classification/score system	8
Progression	7
Epidemiology/etiology	6
Review	5
Surgical outcomes	2
Radiology/imaging	1

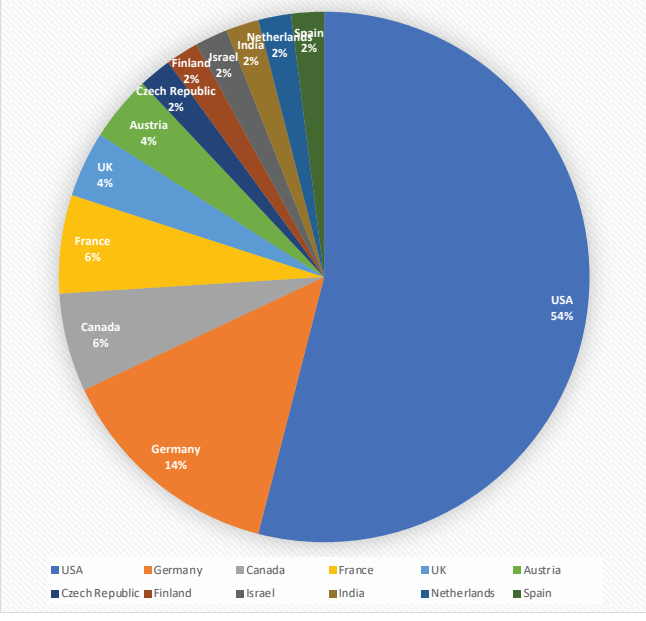

Figure 1. Publications by country

Table 3. Publishing institutes

Institute	Number of publications
Mayo Clinic	5
Yale University School of Medicine	3
University Heidelberg	3
University of Vienna	2
Harvard Medical School	2
University of Illinois at Chicago	2
University of Pittsburgh	2
University of Arkansas for Medical Sciences	2
Cleveland Clinic	2
Others (27 different institutes)	27

Table 4. SCImago Journal & Country Rank, with Scopus data

Journals	Number of publications	Cites/doc. (2 years)	Total docs. (2020)	Total cites (2020)
Journal of Neurosurgery	10	3.16	543	5314
International Journal of Radiation Oncology Biology Physics	5	3.48	584	6588
Neurosurgery	5	2.19	654	3032
American journal of surgical pathology	4	5.36	208	3719
Journal of neuro-oncology	3	3.63	282	3971
Cancer	2	4.63	727	9435
Surgical neurology	2	1.12	409	616
Proceedings of the National Academy of Sciences	2	9.56***	4191**	113782*
Average		4.14	949.7	18307.1

*Most published documents, **Most cited, ***Most cited/document

According to the Thomson ISI Web of Science® Database data, recently a significant increase has been observed in the number of articles on meningioma. In the early 2000s, approximately 500 articles on meningioma were published per year, while recently, this number has approached 1500 per year. Considering the publications year of the 50 most cited articles, it was seen that most articles (38%) were published between 2000-2009. Since our bibliometric study is mostly based on the number of citations, this time interval has been accepted as normal, since it takes time to publish the articles, capture sufficient interest, organize a new study, and publish this study as well. A review of other bibliometric studies also showed that the cited articles were mostly published in the same period (6,10-14).

As far as the journals in which the most cited articles were published are concerned, the Journal of Neurosurgery, International Journal of Radiation Oncology Biology Physics, Neurosurgery, American Journal of Surgical Pathology, Journal of Neuro-oncology, Cancer, Surgical Neurology, and Proceedings of the National Academy of Sciences (PNAS) are the leading ones, respectively (Table 4). Ten of the most cited articles (Table 4) and the most cited article (Table 1) were published in the Journal of Neurosurgery. This Journal is one of the most important sources for the international neurosurgery community. Having examined other journals, we noted that they included oncology as well as neurosurgery journals. This is because meningioma is a subject studied by radiation oncology and medical oncology physicians as well as by neurosurgery physicians. It is recommended that researchers interested in this subject should be cognizant of these journals. Additionally, it has been observed that the journal named PNAS has a higher number of total citations and citations per document compared to the other journals (Table 4).

CONCLUSION

In this study, we used bibliometric analysis methods to present a scientific summary of the 50 most cited articles on meningioma, which has been increasingly studied in the literature, published between 1970-2022. This summary reveals the contributions to this topic by journals, countries, authors, and institutions. Some important publications and journals have been identified for researchers. This bibliometric study provides a collection of data that will help design future research on meningiomas more efficiently, identify gaps, and develop new approaches.

ETHICS

Ethics Committee Approval: All procedures performed were in accordance with the 1964 Helsinki Declaration. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent: For this type of study formal consent is not required.

Authorship Contributions

Surgical and Medical Practices: Ö.Ö., Concept: Ö.Ö., O.B., Design: Ö.Ö., Data Collection or Processing: Ö.Ö., Analysis or Interpretation: Ö.Ö., Literature Search: Ö.Ö., Writing: Ö.Ö.

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Research

Whole-body MRI in Pediatric Patients with Chronic Recurrent Multifocal Osteomyelitis

Kronik Tekrarlayan Multifokal Osteomiyelitli Pediatrik Hastalarda Tüm Vücut MRG

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ABSTRACT

Objective: To evaluate the clinical and radiological findings of the patients with chronic recurrent multifocal osteomyelitis (CRMO) and to present the benefits of using whole-body magnetic resonance imaging (WBMRI) in these patients and the changes we have made in the technique.

Methods: A total of 45 patients who underwent WBMRI between 2017 and 2021 were included in the study. All WBMRI scans included coronal short tau inversion recovery (STIR), coronal T1W, and sagittal spinal STIR sequences. The examination time was 40 min on average. All WBMRIs were evaluated at two different time. At first assessment, only coronal STIR images were evaluated in all patients. In the second assessment, the same patients evaluated with all the sequences. The contribution of coronal T1W and sagittal STIR sequences to the diagnosis was investigated by comparing the first evaluation with the second evaluation. Thirty five patients were diagnosed with CRMO. The remaining 10 patients had other inflammatory, infective, and neoplastic diseases. The diagnosis of 15 patients with CRMO was based on bone marrow biopsy results. Also, biopsy was performed in 10 patients diagnosed as non-CRMO.

Results: Most of the patients had multifocal bone lesions, particularly in the metaphyses adjacent to the epiphyseal region. The bones of the lower extremities were the most commonly affected. The mean delay in diagnosis was 17 months (0-96), and the follow-up period was 20 months (1-47) in a total of 35 patients, with a recurrence rate of 28%. In most patients (88%), lesions could be identified from coronal STIR images alone at the initial evaluation. However, in 5 patients whose diagnosis was missed when evaluated only from coronal STIR images, lesion identification and possible preliminary diagnosis were detected only with coronal T1W and sagittal STIR images in the second look.

Conclusion: WBMRI is an important examination of systemic diseases such as CRMO that involve multiple sites. In addition to coronal STIR sequences, coronal T1-weighted and sagittal STIR sequences are important in identifying other infective-inflammatory diseases and particularly hematological malignant processes in the differential diagnosis of CRMO.

Keywords: Pediatric radiology, chronic nonbacterial osteomyelitis, chronic recurrent multifocal osteomyelitis, CRMO, whole-body MRI

ÖZ

Amaç: Kronik tekrarlayan multifokal osteomiyelitli (CRMO) hastaların klinik ve radyolojik bulgularını değerlendirmek ve bu hastalarda tüm vücut manyetik rezonans görüntüleme (WBMRI) kullanmanın yararlarını ve teknikte yaptığımız değişiklikleri sunmaktır.

Gereç ve Yöntem: 2017-2021 yılları arasında WBMRI uygulanan toplam 45 hasta çalışmaya dahil edildi. Tüm WBMRI taramalarında koronal kısa zamanlı inversiyon düzelme (STIR), koronal T1W ve sagital spinal STIR sekansları kullanılmıştır. İnceleme süresi ortalama 40 dakika idi. Tüm WBMRI'ler iki farklı zamanda değerlendirildi. İlk bakıda tüm hastalarda sadece koronal STIR görüntüleri değerlendirildi. İkinci bakıda aynı hastalara ait tüm sekanslar değerlendirildi. Birinci değerlendirme ile ikinci değerlendirme karşılaştırılarak koronal T1W ve sagital STIR sekanslarının tanıya katkısı araştırıldı. Otuz beş hastaya CRMO teşhisi konuldu. Geri kalan 10 hastanın diğer enflamatuvar, enfektif ve neoplastik hastalıkları vardı. CRMO'lu 15 hastanın tanısı kemik iliği biyopsi sonuçlarına dayanıyordu. CRMO tanısı alan diğer 20 hastada kesin tanı, diğer hastalıkları dışlayan klinik ve radyolojik bulguların varlığında konulmuştur.

Bulgular: Hastaların çoğunda özellikle epifiz bölgesine komşu metafizlerde multifokal kemik lezyonları mevcuttu. En sık alt ekstremite kemikleri etkilenmişti. Toplam 35 hastada ortalama tanı gecikmesi 17 ay (0-96), takip süresi 20 ay (1-47) olup, nüks oranı %28 idi. Hastaların çoğunda (%88), lezyonlar ilk bakıda sadece koronal STIR görüntülerinden bile tanımlanabilmiştir. Ancak sadece koronal STIR görüntülerinden değerlendirildiğinde tanısı atlanan 5 hastada lezyon tanımlaması ikinci bakıda değerlendirilen koronal T1W ve sagital STIR görüntüleri ile mümkün olmuştur.

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ÖZ

Sonuç: WBMRI çekim süresinin uzunluğu ve çocukların uyumu açısından zor bir inceleme yöntemidir. Doğru teşhis ve tedavi için gerekli tüm sekansların yapılması esastır. CRMO'nun ayırıcı tanısında koronal STIR sekanslarına ek olarak koronal T1W ve sagital STIR sekansları diğer enfektif-enflamatuvar hastalıkları ve özellikle hematolojik malign süreçleri belirlemede önemlidir.

Anahtar Kelimeler: Pediatrik radyoloji, kronik bakteriyel olmayan osteomiyelit, kronik tekrarlayan multifokal osteomiyelit, CRMO, tüm vücut MRG

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is a subacute and chronic idiopathic autoinflammatory bone disorder also known as sterile non-bacterial osteomyelitis.

CRMO is characterized by exacerbation and recovery periods with clinical findings and affecting children and adolescents. Despite advances in imaging and microbiological diagnostic techniques and a significant increase in the number of cases over the past decade, the true incidence of CRMO is not yet fully known.

Non-infectious osteomyelitis can be observed in several inherited monogenic autoinflammatory conditions, such as the juvenile form of synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome (SAPHO), Majeed syndrome, pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome, and deficiency of IL-1R antagonist syndrome (1).

Long-term clinical follow-up with whole-body magnetic resonance imaging (WBMRI) may be needed until the patient is in radiological remission or a steady-state is achieved.

Non-steroidal anti-inflammatory drugs, immunosuppressive drugs, and biological agents are used for treating CRMO. Long-term clinical follow-up with WBMRI may be required until the patient is in radiological remission or a steady state is achieved.

Although CRMO is classified in the benign group, it significantly impairs the quality of life of patients due to recurrent symptoms and permanent sequelae. The diagnosis of exclusion was based on clinical presentation, imaging findings, and culture-negative bone biopsies (2,3). Direct radiographic findings are characteristic but not pathognomonic. It may appear completely normal, particularly in the early stages of the disease.

Bone surveys, scintigraphy, and positron emission tomography are generally used for whole-body imaging. However, all of these modalities involve ionizing radiation. WBMRI is used less frequently in children than in adults because of the need for sedation in younger age groups. Among the non-oncological applications of WBMRI, the most important ones are rheumatological diseases, including multifocal recurrent osteomyelitis, arthritis, dermatomyositis, connective tissue diseases, and fever of unknown origin (4). In CRMO, the characteristic patterns of bone involvement and roadmap for possible biopsy can be determined using WBMRI (Figure 1). Furthermore, the response to treatment can be evaluated, and complications can be identified.

There is no standard technique for WBMRI, and the aim is to achieve maximum coverage of the body with the minimum number of images in the shortest possible time. Patients are usually scanned in the supine position with their arms on the sides and legs extended (4). Scanning is performed in the coronal plane to cover most of the body. However, it has a lower sensitivity for the head and thorax than axial plane scans. As in many centers, the main sequence of the examination is the coronal short tau inversion recovery (STIR). Although there is no consensus, one or more of the coronal T1-weighted (T1W), sagittal T2, STIR, T1W, and diffusion-weighted imaging (DWI) sequences can be used in addition to coronal STIR images. T1W images are necessary to better evaluate bone marrow involvement, especially in hematological malignant processes. Therefore, sagittal plane sequences can be added to better assess the vertebral column (5,6).

In this study, we evaluated the use of WBMRI in the clinical and radiological evaluation of patients with CRMO patients and the benefits of changes in the technique we used for diagnosis.

METHODS

Data of 45 patients who presented to the pediatric rheumatology clinic and underwent WBMRI between January 2017 and December 2021 were retrospectively screened. Of these, 35 patients diagnosed with CRMO were included in this study. Ten patients were excluded because they were diagnosed with other, infectious, rheumatological, and hematological diseases. This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (decision no: 283, date: 30.09.2021).

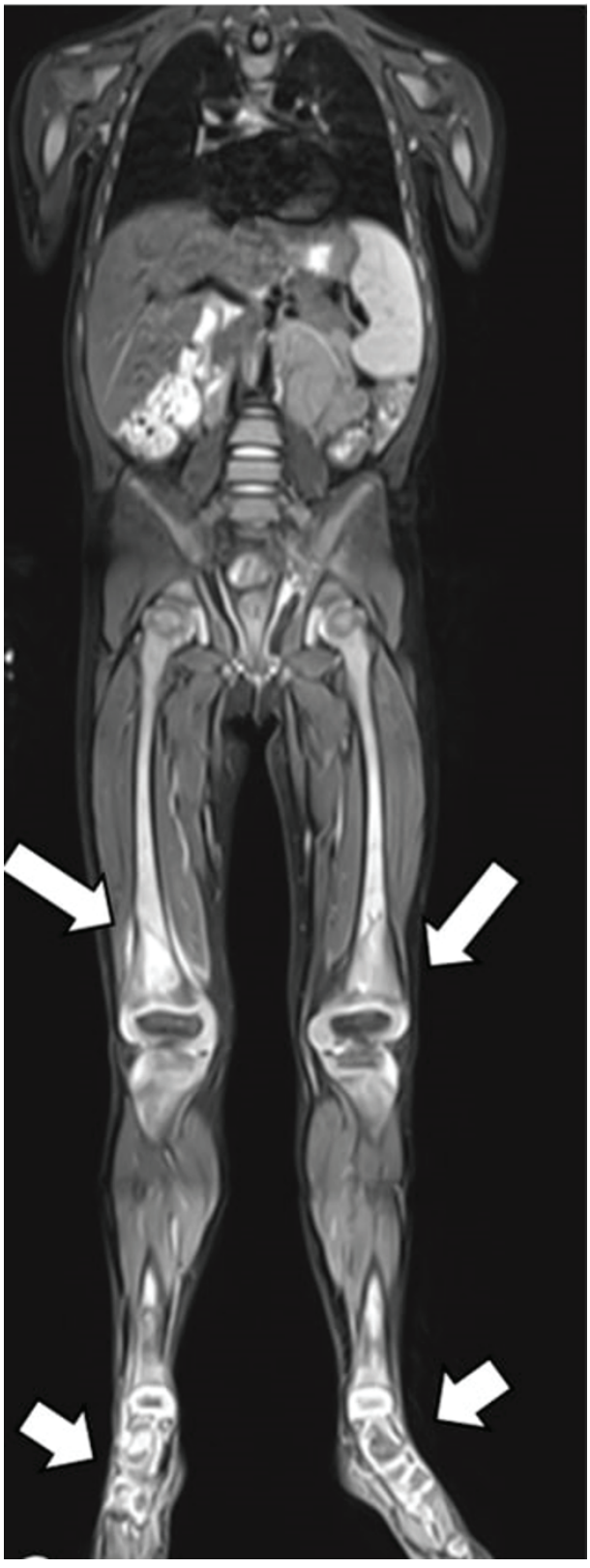

Figure 1. In the whole body coronal STIR image shows diffuse T2W hyperintense pathological signal changes are observed in the distal diaphyseal parts and metaphyses of the bilateral femur and tibia. Also diffuse involvement is observed in the tarsal bones

STIR: Short tau inversion recovery

Patients' clinical, laboratory, and pathological findings were obtained from their electronic files. The radiological data of the patients were re-evaluated using the picture archiving communication system and classified. Plain radiography, computed tomography (CT), and MRI of the patients were completely re-evaluated by a pediatric radiologist with 15 years of experience in radiology.

All WBMRIs were evaluated at two different time. At first assessment, only coronal STIR images were evaluated in all patients (Figure 1). It was then evaluated in the same patients with all their sequences, including coronal T1W and sagittal STIR images. The contribution of coronal T1W and sagittal STIR sequences to the diagnosis was investigated by comparing the first evaluation with the second evaluation.

The radiologic diagnosis of CRMO was based on the presence of at least one lesion consistent with osteomyelitis with radiological and/or histopathological features, excluding infectious, inflammatory, and oncological diseases.

The final diagnosis of 15 patients with CRMO was based on bone marrow biopsy results. In the other 20 patients diagnosed with CRMO, the final diagnosis was made in the presence of clinical and radiological findings, excluding other diseases.

Technical Details of the Radiological Evaluation

Depending on the patient's height, the number of stations scanned in the coronal plane was between five and seven. Additionally, two stations were used to visualize the spine in sagittal STIR images. The images were combined without repositioning to shorten the scanning time.

We analyzed the STIR and T1W sequences in the coronal plane. Additionally, sagittal STIR images of the vertebral column were obtained at the two stations.

The same coil and precisely matched slice selection gradients were used at each station to generate automatic image alignment and whole-body images after the acquisition.

Only two patients were examined under anesthesia. Average shooting time was 35-40 min.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 21. Percentages, medians, and minimum and maximum values were used, where appropriate, to present descriptive statistics.

RESULTS

The main demographic and clinical characteristics of the 35 pediatric patients are included in Table 1. Most patients had multifocal bone lesions at the time of diagnosis. Unifocal involvement was observed in four patients. The distribution of bone lesions is shown in Table 2 (Figure 2). Most patients had periphyseal bone lesions, particularly in the metaphyseal region. In 40% of the patients, only bone marrow edema was detected on MRI, and no abnormal radiological findings were observed on direct radiography or CT, if performed. The mean follow-up period was 20 months (standard deviation, 14 months). Recurrence was observed in 10 patients.

In nine patients (25.7%), there was soft tissue inflammation and periosteal reaction accompanying bone lesions. One patient had osteoporosis and two had vertebral insufficiency fractures (Figure 2). Fourteen patients (40%) had sacroiliitis, four (11.4%) had palmoplantar pustulosis, one (2.9%) had psoriasis, and one (2.9%) had inflammatory bowel disease.

Table 1. Demographic, clinical, and laboratory findings of patients with non-bacterial chronic osteomyelitis

	Total (n=35)
Demographics	
Male (%)	23 (65.7%)
Female (%)	12 (34.3%)
Age at disease onset, years, median (range)	11.8 (5-17)
Delay in diagnosis, months, median (range)	17.4 (0-96)
Follow-up, months, median (range)	19.8 (1-47)
Symptoms	
Bone pain	35 (100%)
Swelling	10 (28.5%)
Limping	9 (25.7%)
Fever	1 (2.8%)
Laboratory findings	
Leukocytes $\times 10^3/mm^3$, range	7.6 (4.2-14)
Erythrocyte sedimentation rate, mm/h, range	27.9 (2-100)
C-reactive protein, mg/dL, range	7.7 (0-58)
Positive antinuclear antibodies, n (%)	8 (22.8)
HLA-B27 positive, n (%)	7 (20)
Syndromic patients	4 (11.4)
SAPHO, n (%)	3 (8.6)
Majeed, n (%)	1 (2.9)

SAPHO: Synovitis, acne, pustulosis, hyperostosis, and osteitis, HLA: Human leukocyte antigen

The unilateral hip dislocation developed in one patient. None of the patients had any clinical or radiological evidence of enthesitis. Three patients were diagnosed with SAPHO, and one with Majeed syndrome.

Joint involvement was present in 20 patients, with some involvement in more than one joint. The sacroiliac joint was the most commonly involved joint, followed by the knee, the sternoclavicular joint, and the ankle (Table 3).

Analysis of biopsy samples revealed osteomyelitis with negative culture results. A mixed inflammatory pattern associated with sclerosis was also observed.

In the WBMRI evaluation of 45 patients, radiological data were insufficient for diagnosis in 5 patients who were evaluated first with coronal STIR. Pathological findings that could not be detected only when evaluated with coronal STIR images could be evaluated after coronal T1W and sagittal STIR images were examined. Of these 5 patients, 2 were diagnosed with acute lymphoblastic leukemia (ALL), one with acute myeloid leukemia (Figure 3), one with brucellous spondylodiscitis, and one with IgG4-related spondylodiscitis (Figure 4).

DISCUSSION

If clinical symptoms are compatible with CRMO, WBMRI should be performed to evaluate multifocal bone lesions, including nonpainful silent lesions. WBMRI is useful not only for diagnosis but also for follow-up and in the detection of possible growth disorders and deformities (7,8). Our study also showed that in addition to routinely applied coronal STIR sequences, the addition of coronal T1W and sagittal STIR images is very valuable in differential diagnosis.

WBMRI is a screening tool that is primarily used for detecting bone marrow edema. Coronal STIR imaging is therefore essential. Some studies have suggested adding T1W and DWI images to the evaluation. In addition, the sagittal plane examination is recommended to evaluate the spinal vertebral column (5,9,10). Damasio et al. (9) stated that T1 imaging is necessary to distinguish between normal bone marrow signals and lesions. The red bone marrow and a CRMO lesion are both hyperintense on STIR images, but the former has an intermediate signal, while the latter is hypointense on T1W images. Additionally, on T1W images, fat, blood products, and proteinaceous material can be differentiated (9,11). There are limited studies on the use of DWI for CRMO. The interpretation of DWI findings can be difficult because of the heterogeneous bone marrow signals in children. However, it may also be useful for differentiating malignant lesions (12,13). In our experience,

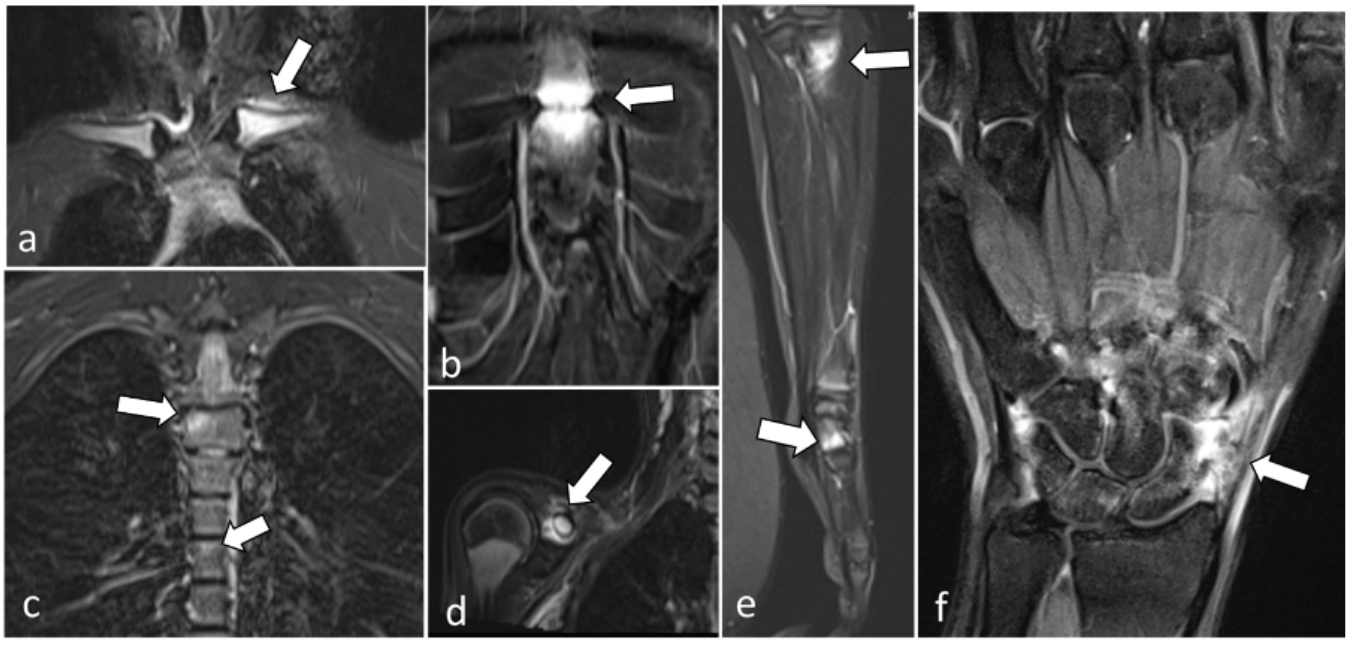

Figure 2. Whole-body magnetic resonance images of a 15-year-old male with axial skeleton and upper extremity involvement. Coronal STIR images show findings of osteitis in the metaphyseal areas adjacent to the physis line in the left clavicle (a), sternum (b), vertebrae (c), coracoid process (d), ulna (e) and carpal bones (e, f)
STIR: Short tau inversion recovery

Table 2. Distribution of the affected bones on magnetic resonance imaging

Affected bones	n (%)
Upper extremity	7 (20)
Humerus	6 (17.1)
Radius	3 (8. 6)
Ulna	1 (2.9)
Carpal/metacarpal bones	4 (11.4)
Lower extremity	**33 (94. 2)**
Femur	23 (65.7)
Tibia	30 (85.7)
Fibula	2 (5.7)
Tarsal/metatarsal bones	23 (65. 7)
Axial skeleton	**18 (51. 4)**
Mandibula	1 (2.9)
Clavicle	8 (22.8)
Scapula/coracoid process	8 (22.8)
Sternum	6 (17.1)
Vertebra	6 (17.1)
Pelvic bones	17 (48.6)

Table 3. Distribution of patients with arthritis

Joints with arthritis	n (%)
Sacroiliitis	14 (40%)
Knee	6 (17.1%)
Sternoclavicular	5 (14.2%)
Ankle	4 (11.4%)
Temporomandibular	2 (5.7%)
Hip	2 (5.7%)
Tarsometatarsal	1 (2.8%)
Talonavicular	1 (2.8%)
Talocalcaneal	1 (2.8%)

it is easier to exclude possible hematological pathologies by adding T1W sequences to STIR images if the patient is scanned without anesthesia and can tolerate a long duration. Hematological malignancies such as leukemia and lymphoma may be confused with CRMO because they may present with abnormal bone marrow. However, in these diseases, rather than edema, focal or extensive bone marrow replacement is observed (14). T1W images are also very useful in differentiating pathologies from the normal red marrow in children (Figure 3). In our patient group, bone marrow blastic infiltration in two patients who could be considered completely normal when coronal STIR images were examined, could be understood from coronal T1W images. The diffuse bone marrow signal reduction in T1W images suggested hematological malignant involvement, and these patients were quickly diagnosed with ALL by bone marrow biopsy.

Additionally, we had the opportunity to evaluate the vertebral columna better in sagittal STIR images. Of the

pathological signal changes, compression fractures, disc and spinal canal pathologies can be better defined. Two patients with spondylodiscitis and one patient with spinal granulocytic sarcoma could be detected by sagittal STIR images in our study.

The average scan time for WBMRI has been reported to be 40 min in previous studies. In our study, the total time of WBMRI varied between 30 and 45 min, depending on the size of the child.

In the literature, the average age of patients at diagnosis of CRMO is 9-11 years, and girls are affected more than boys (2,13,15). In our study group, the mean age at diagnosis was 12 years, and this was more common in boys (65%). It is difficult to determine the onset of the disease because of insidious and subtle symptoms. In a multicenter study of 178 patients, Wipff et al. (16) reported that CRMO was twice as common in the female group, the mean symptom onset year was 9.8 years, the mean age at diagnosis was 16.4 years, and the diagnostic delay time was 17.3 months. These periods decrease over time as the disease becomes more recognizable. In our study, the mean age at diagnosis was 11.8 years, and the mean delay in diagnosis was 17.4 months.

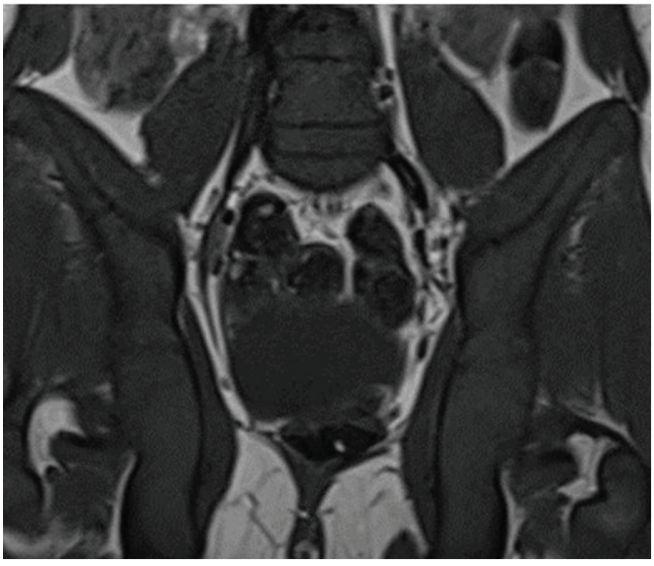

Figure 3. Coronal T1-weighted image of a nine-year-old male patient diagnosed with acute lymphocytic leukemia, showing a markedly decreased T1 signal secondary to the diffuse infiltration of the bone marrow

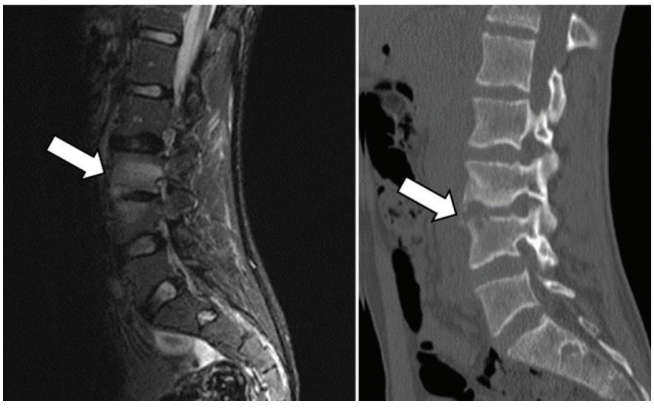

Figure 4. MRI and CT of 17-year-old male patient, inflammatory signal changes are observed in the L3_L4 disc and the vertebral end plateaus facing the disc in sagittal STIR images. There is moderate loss of height in the disc and lytic changes in the bone tissue in the vertebra end plateaus

MRI: Magnetic resonance imaging, CT: Computed tomography, STIR: Short tau inversion recovery

The typical radiological findings of CRMO are multifocality and involvement of the juxtaphyseal/periphyseal areas,

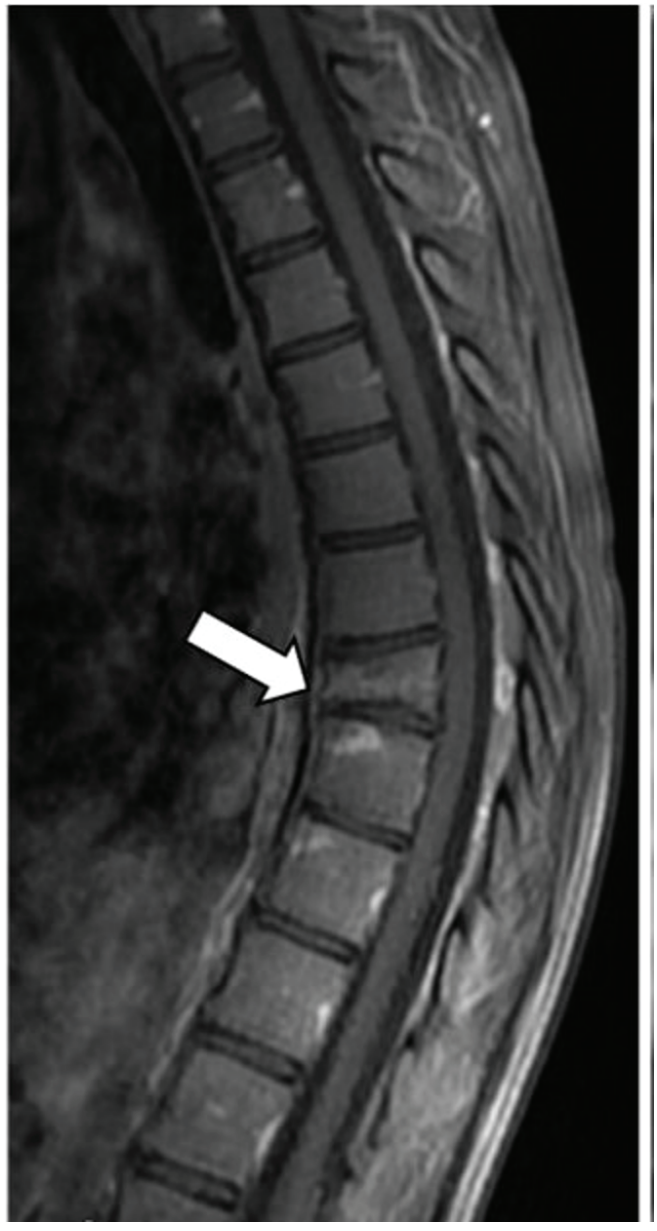

Figure 5. Sagittal STIR images of a 16-year-old girl presenting with a compression fracture in the T8 vertebra and bone marrow edema in the T9 and T10 vertebra corpus superior end plateaus

STIR: Short tau inversion recovery

particularly in the metaphyses. Most bone lesions are located in the tibia, followed by the femur, appendiceal, and axial skeleton (7,17). In our study, the bones of the lower extremities were the most affected body regions, consistent with the literature. In this study, relapse was observed in 28% of the patients during the clinical follow-up. The lower rates of relapse compared with those in the literature may be related to the treatment and follow-up time.

Although CRMO is the most common disease affecting 1/3 of the medial clavicle, clavicular involvement is atypical in bacterial osteomyelitis. In our study, clavicular involvement was present in eight patients (~23%). In some studies, up to 30% of the lesions were reported to be located in the clavicle in patients with CRMO (18).

Spinal involvement is less common than the involvement of long tubular bones, but it can complicate CRMO cases due to pathological fractures. Spinal involvement has recently been recognized as a typical feature of CRMO, with a reported prevalence of up to 30% (16,19,20). In 23 articles, the incidence of spinal involvement in children with CRMO varied between 2% and 43% (21). It can be difficult to differentiate CRMO spinal lesions from bacterial spondylitis or spondylodiscitis. Disc involvement is not expected in CRMO; however, rare cases of CRMO involving the disc have been described (7,20,22). In our study group, spinal vertebral involvement was present in six (17%) patients (Figure 5). Compression fracture complications secondary to thoracic vertebral involvement developed in two of our patients (Figure 2).

Similar to previous studies, multifocal bone lesions were observed in the majority of our patients. The affected bones in the four patients with unifocal involvement were the tarsal bones, fibula, and mandible. Gaal et al. (23) evaluated the data of 22 patients with mandibular involvement who were diagnosed with CRMO and reported that 18 patients had unifocal lesions.

A standard WBMRI protocol was not used in any patient. Biopsy was not undertaken in ten cases due to the typical clinical presentation of CRMO. Since spontaneous remission may occur in patients with CRMO, some patients did not attend their follow-up, and therefore, complete data could not be obtained concerning their treatment and recovery processes.

CONCLUSION

CRMO is a multifocal autoimmune disease that often presents as metaphyseal bone lesions. Recently, CRMO has been increasingly detected using WBMRI. In this study, we discuss the different and overlapping features of our cases in relation to the literature. WBMRI is important for both the diagnosis and follow-up of CRMO with recurrent attacks and multifocal bone involvement. In addition to coronal STIR images, which constitute an essential component of WBMRI, coronal T1W and spinal sagittal STIR images should be included in the evaluation of differential diagnosis of non-bacterial chronic osteomyelitis.

Acknowledgements: We would like to thank the doctors at the Pediatric Clinic of Ümraniye Training and Research Hospital.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (decision no: 283, date: 30.09.2021).

Informed Consent: Retrospective study.

Authorship Contributions

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

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Research

Risk Factors for Complications in Trochanteric Femur Fractures Treated with Dyna Locking Trochanteric Nail

Dyna Locking Trokanterik Çivisi ile Tedavi Edilen Trokanterik Femur Kırıklarında Komplikasyonlar için Risk Faktörleri

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ABSTRACT

Objective: The propose of this study was to asses the factors leading to complications in trochanteric femoral fractures treated with Dyna locking trochanteric (DLT) nails in geriatric patients, with respect to fracture stability pattern, postoperative reduction, screw placement, tip-apex distance (TAD), bone quality, and patient positioning.

Methods: One hundred sixty nine patients operated using DLT nail, aged 65 years and older with a minimum follow-up of 12 months were screened retrospectively. The fracture patterns were grouped as AO Foundation/Orthopedic Trauma Association (AO/OTA) 31-A1, A2, and A3, and the patients were operated in the supine position using a traction table, in the supine position without using a traction table, or in the lateral decubitus position. Postoperative bone mineral density (BMD) measurements were performed in all patients. The Fogagnolo criteria, modified from Baumgartner, were used to evaluate the fracture reduction, and accordingly, the fracture reduction was subdivided into good, acceptable, or poor. TAD measurements were performed as described by Baumgartner. The position of the lag screw within the femoral head was determined according to Cleveland and Bosworth method, and the central-central and infero-central positions were evaluated as optimal and the other positions as suboptimal.

Results: A total of 57 complications were determined, of which 14 (8.2%) were cut-out, cut-through, and intrapelvic migration of the lag screw and distal peri-implant fractures requiring additional interventions. A statistically significant association was found between suboptimal lag screw placement, decreased BMD, TAD measurement >25 mm, and decreased reduction quality with cut-out, cut-through, intrapelvic migration, and varus collapse. Varus collapse was seen at a significantly low rate in AO/OTA 31-A1 type fractures and in surgeries performed with a traction table ($p=0.004$, $p<0.001$), although there was no association between cut-out, cut-through, intrapelvic migration and fracture type and patient positioning ($p=0.542$, $p=0.632$). The optimal lag screw placement and TAD measurements were statistically significantly better in patients who were treated on a traction table ($p<0.001$, $p<0.001$).

Conclusion: Decreased BMD, suboptimal lag screw position in the femoral head, a TAD of >25 mm, unstable fracture patterns, and poor reduction quality have an impact on complications. Performing the surgical intervention on a traction table ensures more favorable lag screw placement.

Keywords: Trochanteric, femur, fracture, DLT, cephalomedullary, complication

ÖZ

Amaç: Çalışmanın amacı geriatrik hastalardaki Dyna locking trokanterik (DLT) çivisi ile tedavi edilen trokanterik femur kırıklarında komplikasyona neden olan faktörleri kırık stabilite paterni, postoperatif redüksiyon, vida yerleşimi, tip-apeks mesafesi (TAD), kemik kalitesi ve hasta pozisyonu ile ilgili olarak değerlendirmektir.

Gereç ve Yöntem: Altmış beş yaş üzerinde minimum 12 ay takipli DLT çivisi kullanılarak opere edilen 169 hasta retrospektif olarak taranmıştır. Kırık paterni AO Vakfı/Ortopedik Travma Derneği (AO/OTA) 31-A1, A2 ve A3 olarak gruplandırılmış hastalar traksiyon masası ile supin pozisyonda, traksiyon masası kullanılmadan supin pozisyonda ya da lateral dekübit pozisyonunda opere edilmiştir. Hastaların tamamına cerrahi sonrası kemik mineral yoğunluğu (KMY) ölçümü yapılmıştır. Kırık redüksiyonunu değerlendirirken Baumgartner'den modifiye edilmiş Fogagnolo kriterleri kullanılmış ve buna göre kırık redüksiyonu iyi, kabul edilebilir ve kötü olarak gruplandırılmıştır. TAD ölçümleri Baumgartner tarafından tarif edilen

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ÖZ

şekilde yapılmıştır. Lag vidasının femur başı içerisindeki pozisyonu Cleveland ve Bosworth yöntemine göre belirlenmiş ve merkez-merkez, infero-merkez pozisyonlar optimal diğer pozisyonlar suboptimal olarak değerlendirilmiştir.

Bulgular: Çalışmada 57 komplikasyon tespit edilmiştir, bunlardan 14'ü (%8,2) ek müdahale gerektiren lag vidasının cut-out, cut-through ve intrapelvik migrasyonu ile birlikte distal peri-implant kırıklarıdır. Yapılan değerlendirmelerde suboptimal lag vidası yerleşimi, düşük KMY, TAD >25 mm ölçümü ve yetersiz redüksiyon kalitesi ile cut-out, cut-through, intrapelvik migrasyon ve varus kollapsı arasında istatistiksel olarak belirgin ilişki saptanmıştır. AO/OTA 31-A1 tipi kırıklarda ve traksiyon masası ile yapılan ameliyatlarda belirgin olarak düşük oranda varus kollapsı görülmüştür (p=0,004, p<0,001), ancak lag vidasının cut-out, cut-through ve intrapelvik migrasyonu ile kırık tipi ve hasta posizyonları arasında ilişki saptanamamıştır (p=0,542, p=0,632). Optimal lag vidası yerleşimi ve TAD ölçümleri ile traksiyon masasında tedavi edilen hastalar arasında istatistiksel olarak anlamlı ilişki saptanmıştır (p<0,001, p<0,001).

Sonuç: Düşük KMY, femur başına uygun olmayan lag vidası yerleşimi, TAD >25 mm olması, instabil kırık paterni ve kötü redüksiyon kalitesi komplikasyonların ortaya çıkmasında etkilidir. Traksiyon masası kullanılarak yapılan cerrahi müdehaleler ile daha uygun lag vidası yerleşimi sağlanabilir.

Anahtar Kelimeler: Trokanterik, femur, fraktür, DLT, sefalomedüller, komplikasyon

INTRODUCTION

Hip fractures in elderly patients are still a common and challenging issue. Early and appropriate surgical treatment thereby obtaining earlier mobility of these patients is essential to be able to avoid increased rates of complications and mortality (1).

Factors affecting the results of trochanteric hip fractures have been extensively studied in the literature. Bone quality, fracture stability and reduction, and proper selection and placement of the implant, have been defined as important determinants for better outcomes (2).

Intramedullary implants are the most preferred devices if internal fixation is applied to a trochanteric femoral fracture (3). The Dyna locking trochanteric (DLT) nail (U&I corporation, 20, Sandan-ro 76beon-gil, Uijeongbu-si, Gyeonggi-do, Korea) is one of the many intramedullary implants that provides better purchase in the osteoporotic femoral head and neck by using a lag screw with 3 wedge wings, thereby preventing complications.

There are very few published studies have reporting the results of trochanteric femur fractures treated with DLT nails (4,5). The aim of the present study was to evaluate the factors leading to complications in geriatric trochanteric femoral fractures treated with DLT nail, with respect to fracture stability pattern, postoperative reduction, screw placement, tip-apex distance (TAD), bone quality, and patient positioning during surgery.

METHODS

The orthopedic trauma database of a single center was retrospectively searched for patients who had sustained a hip fracture, including the femoral head, neck, peritrochanteric, and subtrochanteric femur fracture between January 2016 and December 2019. Approval was obtained from the Clinical Research Ethics Committee of Marmara University Faculty of Medicine (protocol code: 01.2020.578, date: 21.01.2020). Informed consent was provided by all patients, by their parents/legal guardians.

The study inclusion criteria were as follows:

1) Patients aged >65 years,

2) Followed up for at least 12 months,

3) Acute traumatic trochanteric femur fracture (AO 31-A1, A2, A3),

4) Treated with internal fixation with DLT nail.

The study exclusion criteria were defined as age <65 years, pathological fractures, patients with an associated fracture in the ipsilateral extremity, a follow-up period of less than 12 months, treated with implants other than DLT nail, or X-ray quality unsuitable for radiological evaluation. Data were retrieved from patient files related to age, fracture side, surgery time, blood loss, positioning during surgery, and duration of hospital stay.

The study was conducted on a total of 169 patients who met the criteria, comprising 72 males and 97 females with an average age at the time of injury of 78.6 years (range, 65 to 103 years) (Figure 1).

Surgical Technique

The operations of the patients evaluated in this study were performed by 7 surgeons. All surgeons are highly experienced in hip trauma. DLT nails were used in all cases as the implant for internal fixation. Surgical interventions were performed in three patient positions according to the surgeon's preference: the supine position with a traction table, supine position with manual traction, and lateral decubitus. The fracture reduction was achieved through

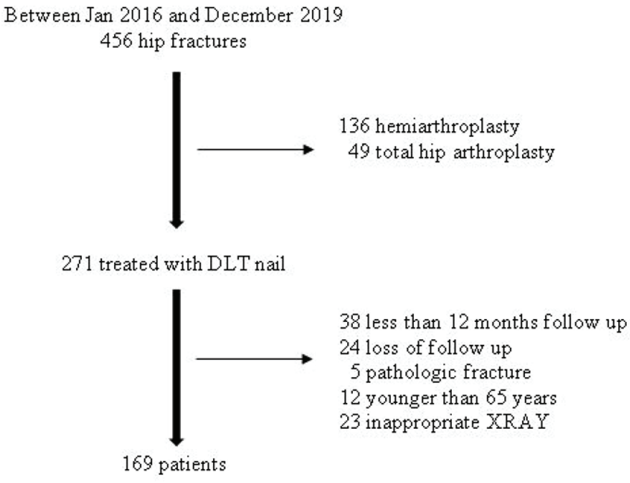

Figure 1. Flowchart showing the inclusion of the patients
DLT: Dyna locking trochanteric

the closed or open technique. Intraoperative fracture reduction and implant position were confirmed using C-arm fluoroscopy.

Radiological Evaluation

Fractures were classified according to the AO/OTA classification on preoperative anteroposterior (AP) and lateral radiographs of the hip (6).

On immediate postoperative AP and lateral radiographs of the hip,

- Fogagnolo criteria modified from Baumgartner were used to evaluate the fracture reduction. The reduction was sub-grouped as good, acceptable, or poor (7).

- Varus and valgus malalignment were evaluated by measuring the neck-shaft angle of both hips, with malalignment accepted as >5° varus or >15° valgus compared to the contralateral hip (8).

- TAD was measured as described by Baumgartner (9).

- The position of the lag screw was determined according to the Cleveland and Bosworth method, in which central-central and inferior-central placement of the lag screw is accepted as the optimal position, and any other placement is suboptimal (10).

All fracture classifications, radiological evaluations, and measurements were performed by an independent observer.

Follow-up Protocol

Immediate weight-bearing as tolerated was permitted for all patients. Follow-up examinations, both radiological and clinical, were carried out at 3-week intervals until the third month, and after that every 3 months until the end of the year. The patients were informed that if any complaints developed, they should attend immediately without waiting for a routine follow-up appointment. In all patients, bone mineral density (BMD) measurements were taken using dual energy X-ray absorptiometry within 3 weeks after surgery.

Statistical Analysis

Data were analyzed using SPSS for Windows (version 15.0) software (SPSS Inc., Chicago, IL, USA). The conformity of the data to a normal distribution was evaluated using the Kolmogorov-Smirnov test. For assessing the study data, in addition to descriptive statistical methods (average, standard deviation, median, frequency, ratio, minimum, maximum), the Independent samples t-test was used to compare normally distributed parameters between the groups and the Kruskal-Wallis test and Mann-Whitney U test were used to compare non-normally distributed parameters between the groups in the comparison of quantitative data. Categorical data were compared using the chi-square and Fisher's Exact tests. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The data of the patients, including fracture classification and reduction type, reduction quality of the fracture, lag screw position in the femoral head, TAD measurements, surgical position, and BMD measurements are shown in Table 1.

Complications

A total of 57 complications were determined, of which 14 (8.2%) were cut-out, cut-through, and intrapelvic migration of the lag screw, and distal peri-implant fractures requiring additional surgical interventions (Table 2).

Cut-out, Cut-through and Intrapelvic Migration

These complications were determined in 11 patients (6.5%), comprising 9 cut-out, 1 cut-through, and 1 intrapelvic migration, which required revision (Figure 2, 3). These complications were seen at a mean 3.6±4 months (range, 2 weeks -15 months) after surgery.

Varus Collapse

Varus collapse was accepted as a difference of >5° between the immediate postoperative and final follow-up X-ray measurements. Varus complication was the most frequently seen complication, determined in 36 patients at mean 2.5±1 months (range, 3 weeks-5 months) after surgery.

A statistically significant association was found between suboptimal lag screw placement, decreased BMD, TAD measurement >25 mm, and decreased reductin quality,

Table 1. Data related to fracture classification and reduction type, reduction quality of the fracture, lag screw placement in the femoral head, tip-apex distance measurements, patient positioning and bone mineral density measurements

		n	%
Fracture type	31-A1	31	18.3
	31-A2	125	74.0
	31-A3	13	7.7
Patient positioning	Lateral decubitus	48	28.4
	Supine, manual traction	38	22.5
	Supine, traction table	83	49.1
Reduction type	Open	4	2.4
	Closed	165	97.6
Reduction quality	Good	47	27.8
	Acceptable	102	60.4
	Poor	20	11.8
BMD	Normal	51	30.2
	Osteopenia	39	23.1
	Osteoporosis	79	46.7
Lag screw placement	Suboptimal	60	35.5
	Optimal	109	64.5
TAD	>25 mm	28	16.6
	≤25 mm	141	83.4

BMD: Bone mineral density, TAD: Tip-apex distance

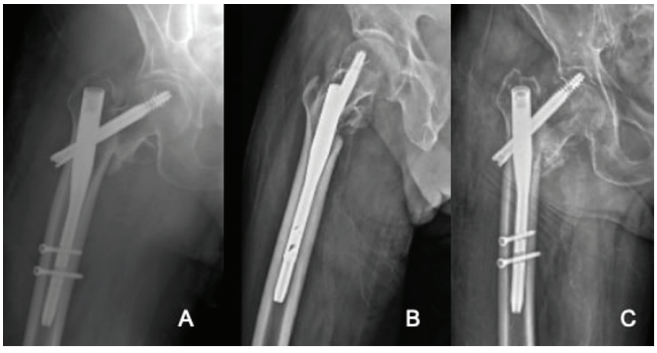

Figure 2 A, B, C. Immediate postoperative X-rays (A, B) showing suboptimal lag screw placement, TAD >25 mm and an acceptable reduction, resulted with cut-out (C) after 3 week
TAD: Tip-apex distance

with cut-out, cut-through, intrapelvic migration, and varus collapse (Table 3). Varus collapse was seen at a significantly low rate in AO/OTA 31-A1 type fractures and in surgeries performed with the use of a traction table (p=0.004, p<0.001). No association was determined between cut-out, cut-through, intrapelvic migration and fracture type and patient positioning (p=0.542, p=0.632) (Table 3).

The optimal lag screw placement and TAD measurements were statistically significantly better in patients who were treated on a traction table compared with the manual traction and lateral decubitus groups (p<0.001, p<0.001) (Table 4).

DISCUSSION

Hip fractures are one of the most common fractures requiring surgical intervention in the aging population and have an important place in routine orthopaedic practice worldwide. It can be defined as a fracture requiring urgent treatment as delayed treatment results in increased mortality rates (11).

The most appropriate implant for use in internal fixation of trochanteric femur fractures remains a matter of controversy (12-14). Osteoporosis and fracture stability are issues affecting whether cephalomedullary nail or extramedullary implants should be used (15). However, cephalomedullary nails are the most frequently preferred implants regardless of the experience of the surgeon, and the use of these nails has become accepted worldwide over the last three decades (3,16). Cephalomedullary nails have biomechanical superiority in respect to axial load sharing compared to extramedullary implants, and therefore have better failure resistance for unstable trochanteric fractures (17-19). In this study, DLT nail

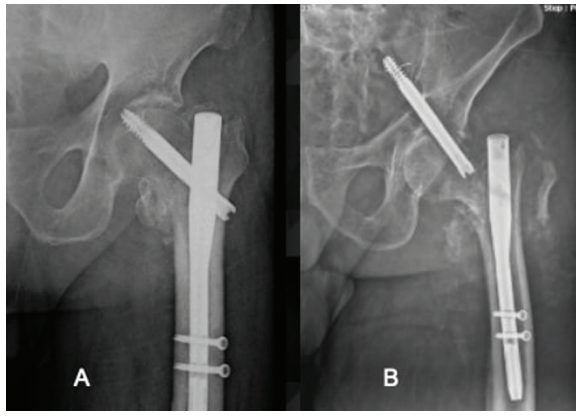

Figure 3 A, B. Cut-through (A) and intra pelvic migration of the lag screw (B) are less commonly seen complications, which are affected from surgeon dependent factors including fracture reduction, lag screw position and TAD
TAD: Tip-apex distance

Table 2. Complications of the patients

Complications			
Cut-out, cut-through and intrapelvic migration	**n (%)**	**Others**	**n (%)**
Cut-out	9 (5.3)	Varus collapse	36 (21.3)
Cut-through	1 (0.6)	Distal peri-implant fracture	3 (1.8)
Intrapelvic migration	1 (0.6)	-	-

Table 3. P-values for factors accompanying to cut-out, cut-through, intrapelvic migration and varus collapse

		Cut-out, cut-through and intrapelvic migration	p-value	Varus collapse	p-value
		n (%)		n (%)	
Lag screw placement	Suboptimal	10 (90.9%)	0.000*	36 (29.3%)	0.000*
	Optimal	1 (9.1%)		0 (0.0%)	
BMD	Normal	0 (0.0%)	0.028*	4 (7.8%)	0.000*
	Osteopenia	1 (9.1%)		6 (15.8%)	
	Osteoporosis	10 (90.9%)		26 (37.7%)	
TAD	≤25 mm	1 (9.1%)	0.000*	20 (14.3%)	0.000*
	>25 mm	10 (90.9%)		16 (88.9%)	
Reduction quality	Good	0 (0.0%)	0.000*	2 (4.3%)	0.000*
	Acceptable	2 (18.2%)		23 (23.0%)	
	Poor	9 (81.8%)		11 (100%)	
Patient positioning	Supine, traction table	1 (9.1%)	0.632*	7 (8.5%)	0.000*
	Supine, manual traction	6 (54.5%)		16 (50%)	
	Lateral decubitus	4 (36.4%)		13 (29.5%)	
Fracture type (AO/OTA)	31A1	1 (9.1%)	0.542*	2 (6.7%)	0.004*
	31A2	8 (72.7%)		28 (23.9%)	
	31A3	2 (18.2%)		6 (54.5%)	

*Chi-square test. BMD: Bone mineral density, TAD: Tip-apex distance, AO/OTA: AO Foundation/Orthopedic Trauma Association

Table 4. Lag screw placement according to the surgical patient positioning

Lateral decubitus		Patient positioning: Supine manual traction	Supine traction table		p-value
		n (%)	n (%)	n (%)	
TAD	≤25 mm	40 (83.3%)	20 (52.6%)	81 (97.6%)	0.000*
	>25 mm	8 (16.7%)	18 (47.4%)	2 (2.4%)	
Screw position	Optimal	30 (62.5%)	10 (26.3%)	69 (83.1%)	0.000*
	Suboptimal	18 (37.5%)	28 (73.7%)	14 (16.9%)	

*Chi-square test. TAD: Tip-apex distance

was used for all patients as the implant for internal fixation. This nail has three wedge wings on the lag screw for better purchase in the osteoporotic femoral head and has the biomechanical advantages of an intramedullary nail (4,5).

Many studies of trochanteric femur fractures in the geriatric patient population have focused on complications after internal fixation (8,20,21). In the current study cut-out, cut -through and intrapelvic migration was determined in 11 patients (6.5%), including 9 cut-out, 1 cut-through, and 1 intrapelvic migration. The cut-out rates are mixed for DLT nail, with a rate of 25% reported in one study, and no cases in another (4, 5). Some risk factors have been well described for cut-out, cut-through, and intrapelvic migration. A meticulous surgical technique including good reduction quality, TAD measurement <25 mm and central-central or inferior-central placement of the lag screw are modifiable and essential factors for avoiding complications and obtaining better surgical outcomes (2,8,22,23). The current study findings were similar to previous reports in the literature, which have shown a significant association between increased cut-out, cut-through, intrapelvic migration and suboptimal screw placement, TAD of >25 mm, and poor reduction quality.

The surgical interventions in the current study were performed in three different surgical positions according to the surgeons preference: supine with a traction table, supine with manual traction, and lateral decubitus position. The use of a traction table resulted in more favorable TAD measurements and lag screw placement compared with manual traction and the lateral decubitus position. Cut-out, cut-through, and intrapelvic migration were also seen to be fewer, but the difference was not statistically significant.

Varus collapse is another frequently seen complication resulting in femoral shortening and alterations in the gait (4,24,25). In a biomechanical study by Tisherman et al. (26), it was reported that distal locking of the nail could prevent collapse in cases with an osteoporotic unstable fracture pattern. Using a helical blade rather than a lag screw, especially in reverse oblique and transverse fractures, has also been suggested as another preventative method against collapse (25). Selecting the appropriate nail

diameter to fill the medulla has a movement-limiting effect, and may therefore slow the rate of varus collapse (27). As using a helical blade and selecting a large nail are methods that provide better purchase in osteoporotic bone, this suggests that BMD has an important impact on varus collapse. The findings of the current study support this view with the determination of a significant association between a higher rate of varus collapse and decreased BMD. The findings of the current study also revealed a relationship between suboptimal screw placement, TAD measurement >25 mm, poor fracture reduction, unstable fracture pattern, and a higher rate of varus collapse. Patients who underwent surgery on a traction table suffered less varus collapse, which could be attributed to more favorable lag screw placement.

Peri-implant fracture is another devastating complication reported at rates of 1.7% and 2.3% in two meta-analyses, and which was seen in 3 (1.8%) patients in the current study (14,28). Distal locking is a controversial issue in peri-implant fractures and has been thought to be due to the nail tip leading to increased stress concentration, and thereby causing secondary fractures (29). However, this hypothesis was disproved by the same author, suggesting that distal locking served to prevent postoperative femoral fractures (30). Using long nails and slotting of the distal tip of short nails has been shown to result in lower rates of peri-implant fracture (31,32). Increased femoral bowing was determined in all 3 patients in the current study. Skála-Rosenbaum et al. (30) stated that increased femoral bowing and the distal tip of the nail touching the anterior femoral cortex may cause fracture through increased stress concentration. As a technical trick, choosing a slightly anterior entry point in the sagittal plane may permit the nail tip to be oriented from anterior to posterior, and thus a space can be provided between the anterior femoral cortex and the distal nail tip.

There were some limitations to this study, primarily the retrospective design, and that only the results of DLT nail were presented without comparison with any other implant. The preoperative functional status, comorbidities, and postoperative functional outcomes of the patients were not assessed. The interventions were performed by several different surgeons. There is need for further prospective, randomized studies comparing the DLT nail with other implants to provide more valuable information. However, this study can be considered of value as it included the largest number of patients treated with DLT nails.

CONCLUSION

The complication rates for DLT nails are comparable to those for other implants. Decreased BMD, suboptimal lag screw position in the femoral head, a TAD >25 mm, unstable fracture patterns, and poor reduction quality impact complications. Performing the surgical intervention on a traction table provides more favorable lag screw placement. The DLT nail can be used safely for internal fixation of trochanteric femur fractures with care taken to apply a meticulous surgical technique.

ETHICS

Ethics Committee Approval: Approval was obtained from the Clinical Research Ethics Committee of Marmara University Faculty of Medicine (protocol code: 01.2020.578, date: 21.01.2020).

Informed Consent: Informed consent was provided by all patients, by their parents/legal guardians.

Authorship Contributions

Surgical and Medical Practices: S.İ., Concept: S.İ., T.O., Design: S.İ., T.O., Data Collection or Processing: S.İ., Analysis or Interpretation: T.O., Literature Search: S.İ., T.O., Writing: S.İ., T.O.

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

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Research

Evaluation of the Presence of *Helicobacter Pylori* in Inflammatory Bowel Disease in Children

Çocuklarda Enflamatuvar Bağırsak Hastalığında *Helikobakter Pilori* Değerlendirilmesi

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ABSTRACT

Objective: The prevalence of *Helicobacter pylori* (Hp) infection in the pediatric patient group is high, but it depends on the geographical structure of the country. Many studies have show that inflammatory bowel disease (IBD) is less affected by Hp infection than the general population. We aimed to evaluate Hp infection in the IBD patient group we followed and but it depends on the geographical structure of the country.

Methods: The files of the patients diagnosed with IBD who were followed-up in our outpatient clinic were retrospectively analyzed, and their diagnosis and presence of Hp in gastroscopic biopsy were recorded.

Results: A total of 50 patients, 44% female (22 patients) and 56% male (28 patients) were included in the study. The mean age of the patients was 15.3 years. In the gastroscopic biopsy results of the patients, Hp was positive in gastric biopsy at a rate of 28% (14 patients). 71.4% (10 patients) of Hp-positive patients had ulcerative colitis (UC), and 21.4% (3 patients) had Chron disease (CD). When all patients were evaluated, most patients (60%) were Hp-negative (30 patients). Among patients with UC (25 patients), Hp positivity was as high as 40% (10 patients). In CD 14% (3 patients) had Hp positivity. Hp positivity was much higher in the UC patient group. No correlation was found between the presence of Hp and polymorphonuclear leukocytes/lymph ratio, mean platelet volume, acute phase markers (C-reactive protein, sedimentation), vitamin B12, and albumin levels. However, when the ferritin means were compared, the ferritin mean of the Hp-positive patients (47.4) was lower than the Hp-negative patients (62.3).

Conclusion: Hp positivity was higher in the IBD patient group, particularly in patients with UC patients. Supporting the literature, Hp positivity was seen less frequently in our IBD patient group than in the general population.

Keywords: Pediatric, inflammatory bowel disease, *Helicobacter pylori*, gastritis

ÖZ

Amaç: Çocuk hasta grubunda *Helikobakter pilori* (Hp) enfeksiyon prevalansı yüksek olup ülkelere ve coğrafik dağılıma göre farklılık göstermektedir. Yapılmış birçok çalışma enflamatuvar bağırsak hastalarının (IBH), genel topluma göre Hp enfeksiyonundan daha az etkilendiğini göstermektedir. Biz bu çalışmamız ile takip ettiğimiz IBH hasta grubunda Hp enfeksiyonunu ve Crohn hastalığı (CH) ile ülseratif kolit (UK) hastaları arasında Hp varlığının oranlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışma hastanemiz polikliniğinde takip edilen IBH tanılı hastaların dosyaları retrospektif olarak incelenerek tanıları, gastroskopik biyopside Hp varlığı kayıt edilmiştir.

Bulgular: Çalışmaya toplam 50 hasta, 22'si kız (%44) ve 28'i erkek (%56) dahil edildi. Hastaların yaş ortalaması 15,3 yaş idi. Hastalar yapılan gastroskopik biyopsi sonuçlarında gastrik biyopside Hp %28 (14 hasta) oranında pozitif idi. Hp pozitif olan hastaların %71,4'ü (10 hasta) UK, %21,4'ü (3 hasta) CH idi. Tüm hastalar değerlendirildiğinde hastaların çoğunluğunda %60'ında Hp negatif (30 hasta) idi. Hp negatif olan hastaların %50'si (15 hasta) CH idi. UK hastaları (25 hasta) içinde Hp pozitifliği %40 (10 hasta) kadar yüksek idi. CH grubunda ise %14 (3 hasta) kadar Hp pozitifliği mevcut idi. Hp pozitifliği UK hasta grubunda çok daha yüksek oranlarda idi. Hp varlığı ile polimorfonükleer lökositler/lenf

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ÖZ

oranı, ortalama trombosit hacmi, akut faz belirteçleri (C-reaktif protein, sedimentasyon), B12 vitamin düzeyi, albumin düzeyleri arasında bir ilişki bulunamadı. Fakat demir ortalamaları kıyaslandığında Hp pozitif olan hastaların demir ortalaması (47,4), Hp negatif olanlardan (62,3) daha düşük idi.

Sonuç: Hp varlığı IBH hasta grubunda, özellikle UK hastalarında daha yüksek oranlarda saptanmıştır. IBH hasta grupları arasında özellikle UK hastalarında Hp pozitifliği daha yüksek oranlardadır. Literatürü destekler şekilde bulunmuştur ki Hp pozitifliği IBH hasta gruplarında genel topluma göre daha düşük oranlardadır.

Anahtar Kelimeler: Çocuk, enflamatuvar bağırsak hastalığı, *helikobakter pilori*, gastrit

INTRODUCTION

Helicobacter pylori (Hp) is the bacterium that most frequently causes disease in the gastrointestinal tract (1). About 50% of the general population was infected with Hp. The prevalence of Hp infection is high in the pediatric patient group, and it differs according to country and geographical distribution (2). While the prevalence of the disease is low in high-income and developed countries (34.7%), it is higher in the middle- and low-income countries (50.8%) (3). In studies conducted in different regions in the literature, while Hp infection is <40% in developed countries, this rate has been reported to be as high as 80-90% in developing regions, especially in regions with low socioeconomic status, crowded living environments, and low-income levels (4). Recent studies have shown that the prevalence of Hp has started to decrease due to the improvement in living standards and the increase in antibiotic use (5). Inflammatory bowel diseases (IBD) are chronic diseases with idiopathic gastrointestinal system inflammation. Crohn's disease (CD) and ulcerative colitis (UC) are important health problems due to their increasing prevalence worldwide (6). Some studies have show that IBDs are less affected by Hp infection than the general population (7). In this study, we aimed to evaluate the Hp infection in the IBD patient group we followed and the distribution of infection in the CD and UC patient groups.

METHODS

The study was conducted by retrospectively examining the files of 50 patients diagnosed with IBD between 2017 and 2021, followed by our outpatient clinic 1. The approval of the study was obtained from the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Research Ethics Committee, date: 4.07.2022 (decision no: 2032). We take informed consent from the patients and their parents. The diagnosis of IBD in the patients was made according to the Porto criteria (8) because of clinical, laboratory, and endoscopic biopsies. Biopsies taken from the patients included in the study were taken from the stomach antrum 2 bx, corpus 2 bx, fixed with 10% formalin, and embedded in paraffin blocks, after hematoxylin eosin and May-Grünwald Giemsa or Masson trichrome staining, Hp colonization was evaluated by examining under a microscope. The presence of Hp was determined by histopathological examination of the biopsy material.

Statistical Analysis

The SPSS (Statistical Package for the Social Sciences) 25.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where appropriate). The Shapiro-Wilk test was used to determine whether the parameters in the study showed a normal distribution. Pearson correlation test was used to determine the relationship between application and control findings in normally distributed parameters. Statistical significance level was taken as 0.05 in all tests.

RESULTS

Fifty patients diagnosed with IBD were included in our study. Of the patients, 22 (44%) were female, and 28 (56%) were male. The mean age of the patients were 15,3 years. A total of 90% (45 patients) of the patients were in Turkish ethnicity and 10% (5 patients) were other ethnicities. Because of the histopathological examination of the gastroscopic biopsy results performed at the time of diagnosis, the presence of Hp in the gastric biopsy was positive in 28% of the patients (14 patients).

71.4% (10 patients) of Hp-positive patients had UC, and 21.4% (3 patients) had CD. Of the Hp-negative patients, 50% (15 patients) had CD and 43.3% (13 patients) had UC (Figure 1).

When all patients were evaluated, the majority of the patients (60%) were Hp-negative (30 patients), and the Hp status was unknown in 12% (6 patients). There were 25 patients with UC, among which Hp positivity was as high as 40% (10 patients). While 88% (22 patients) of these

patients had macroscopic findings compatible with gastritis during the gastroscopic examination, this rate was 67% (14 patients) in CD. There were 21 patients in the CD group, of which 14% (3 patients) had Hp positivity, whereas 71% (15 patients) of these patients were evaluated as Hp-negative. Hp positivity was much higher in the UC patient group.

No correlation was found between the presence of Hp and polymorphonuclear leukocytes/lymph ratio, mean platelet volume, acute phase markers (C-reactive protein, sedimentation), vitamin B12, and albumin levels (Table 1). However, when the mean ferritin levels between Hp-positive and negative patients were compared, the mean ferritin of Hp-positive patients was 47.4 µg/dL, while it was 62.3 µg/dL in Hp-negative patients. The mean ferritin of Hp-positive patients were lower than Hp-negative patients (Figure 2).

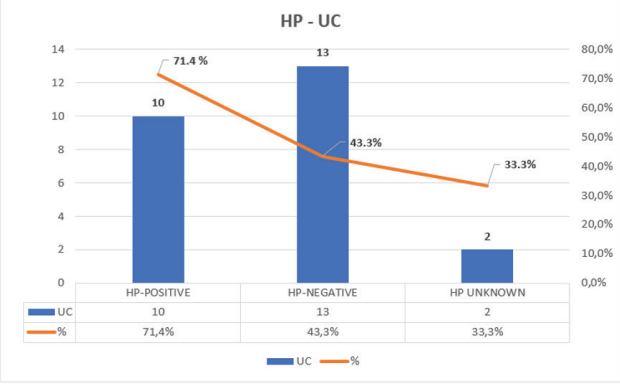

Figure 1. Evaluation of Hp positivity and negativity rates in UC patients
Hp: *Helicobacter pylori*, UC: Ulcerative colitis

Table 1. The correlation between the presence of Hp and PNL/lymph ratio, MPV, acute phase markers (CRP, ESR), vitamin B12, and albumin levels

	Hp-positive	Hp-negative	Unknown
	n=14	n=30	n=6
	Mean (min-max)	Mean (min-max)	Mean (min-max)
PNL/lymph ratio	2.4 (1.2-4.2)	3.1 (0.5-12.5)	1.7 (0.4-3.5)
MPV	7.7 (6.1-10.6)	8.2 (5.9-11.5)	9.2 (6.8-10.8)
CRP	7.7 (0.3-48)	21.5 (0.1-143)	3.4 (0.8-5.8)
ESR	11 (2-30)	13.3 (2-71)	22.3 (9-34)
Vitamin B12 levels (mean)	269	237	432
Albumin (mean)	3.8	3.6	3,4

Hp: Helicobacter pylori, PNL: Polymorphonuclear leukocytes, MPV: Mean platelet volume, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, min-max: Minimum-maximum

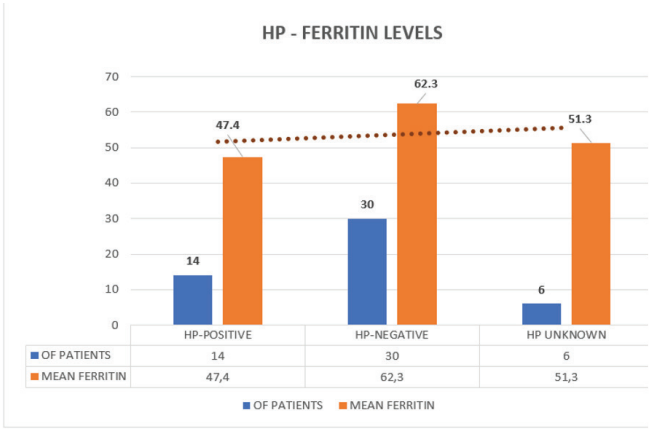

Figure 2. Evaluation of ferritin levels with the presence and absence of Hp
Hp: *Helicobacter pylori*

DISCUSSION

In developing countries such as ours, the prevalence of Hp has been reported to be as high as 60-70% in the childhood age group (9). In our study, in which we evaluated the presence of Hp in IBD, the rate of Hp positivity was 28%. Studies showed an inverse relationship between the presence of Hp and IBD (10). In a few case reports it show that Hp eradication may worsen UC (11).

When the literature is examined, it has been shown that the inverse relationship between Hp infection and IBD is associated with the suppression of proinflammatory responses (12). In a study by Agin et al. (13), the upper endoscopic analysis of different inflammatory disease such as Familial Mediterranean fever it revealed that 50% (14 patients) of the patients had antral gastritis [8 Hp (-) antral gastritis and 6 Hp (+) chronic active gastritis]. This suggests that the inverse relationship stems from these two diseases' socioeconomic and demographic distributions (14).

In our study, 71.4% of Hp-positive patients had UC, whereas 21.4% had CD. The fact that Hp infection was detected more frequently in patients with UC than in CD patients suggested that the frequency of Hp infection may vary in different disease types depending on the type of IBD, different from what was reported in the literature (15). The main study limitation is the small number of patients in the study. The other study restrictions are that the presence of Hp was evaluated as present or absent, and the density of Hp could not be mentioned.

CONCLUSION

Hp infection is an important gastrointestinal infection especially in the pediatric age group with cronic conditions. The protective effect of the Hp infection for some illnesses

is getting much more priority by the time. Hp positivity was higher in the IBD patient group, especially in patients with UC patients. Supporting the literature, Hp positivity was seen less frequently in our IBD patient group than in the general population. Therefore, it should be emphasized that Hp infection should be planned in some special cases and when its treatment is deemed of serious benefit.

ETHICS

Ethics Committee Approval: The approval of the study was obtained from the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Research Ethics Committee, date: 4.07.2022 (decision no: 2032).

Informed Consent: We take informed consent from the patients and their parents.

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

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Research

A Study on Neurosurgery Specialty Theses and Their Publication Status in International Journals

Nöroşirürji Uzmanlık Tezleri ve Uluslararası Dergilerde Yayınlanma Durumları Hakkında Bir Çalışma

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ABSTRACT

Objective: Bibliometric analysis of theses can provide information on the trends and shortcomings in the related scientific field. Several studies have evaluated the specialty theses in different medical disciplines. In this study, we investigated the publication rates of neurosurgery specialty theses in international scientific journals and associated factors.

Methods: Neurosurgery specialty theses completed between 2015 and 2019 was searched in the National Thesis Center of Higher Education Council database. The author, mentor, institution, thesis title, study design, and study topic were extracted. Publications of authors were browsed in the Scopus database in terms of a paper derived from the thesis. Current publication parameters of the author and mentor were also recorded. The publication status of the theses was analyzed regarding author-related factors (publication count, h-index, first-author article), mentor-related factors (publication count, h-index), institution, study design, and study topic.

Results: Two hundred and sixty-one theses were included in this study. The publication rate in a Scopus-indexed journal was 26.8%. Publication counts of author and mentor ($p<0.001$ and $p=0.027$, respectively), h-index of the author ($p<0.001$), first-author article by the author ($p<0.001$), study design ($p=0.009$), and study topic ($p=0.013$) were associated with the publication status of the theses.

Conclusion: The publication rate of neurosurgical theses sits above average compared to other medical disciplines. The most important factor for the publication of a thesis appears to be the academic activity of the author. Regardless, still a high percentage of neurosurgery theses have not been published, and their contribution to cumulative scientific knowledge remains limited.

Keywords: Thesis, publication, neurosurgery, index

ÖZ

Amaç: Tezler üzerinde yapılan bibliyometrik analizler ilgili bilim dalındaki eğilimler ve kısıtlılıklar hakkında bilgi sağlayabilir. Birçok çalışma farklı tıp disiplinindeki uzmanlık tezlerini incelemiştir. Bu çalışmada, nöroşirürji uzmanlık tezlerinin bilimsel dergilerde yayınlanma oranlarını ve ilişkili faktörleri inceledik.

Gereç ve Yöntem: 2015 ile 2019 yılları arasında tamamlanmış nöroşirürji uzmanlık tezleri Yüksek Öğretim Kurumu Ulusal Tez Merkezi veritabanında arandı. Yazar, danışman, tez başlığı, çalışma tipi, çalışma konusu toplandı. Scopus veritabanında yazara ait yayınlar tezden türetilmiş yayın varlığı açısından tarandı. Ek olarak yazar ve danışmana ait güncel yayın parametreleri de kaydedildi. Tezlerin yayınlanma durumu yazarla ilişkili faktörler (yayın sayısı, h-indeks, ilk isim yayın), danışmanla ilişkili faktörler (yayın sayısı, h-indeks), kurum, çalışma tipi ve çalışma konusu açısından değerlendirildi.

Bulgular: İki yüz altmış bir tez bu çalışmaya dahil edildi. Scopus'ta indekslenen dergilerde yayınlanma oranı %26,8 idi. Yazar ve danışmanın yayın sayısı (sırasıyla $p<0,001$ ve $p=0,027$), yazarın h-indeksi ($p<0,001$), yazara ait ilk isim yayın ($p<0,001$), çalışma tipi ($p=0,009$), ve çalışma konusu ($p=0,013$) tezlerin yayınlanma durumu ile ilişkili bulundu.

Sonuç: Nöroşirürji tezlerinin yayınlanma oranı diğer tıp disiplinleri ile karşılaştırıldığında orta sıraların üstünde yer almaktadır. Bir tezin yayınlanmasındaki en önemli faktör yazarın akademik aktivitesi olarak gözükmektedir. Yine de tezlerin büyük bir oranı yayınlanmamakta ve bilimsel bilgi birikimine katkısı sınırlı kalmaktadır.

Anahtar Kelimeler: Tez, yayın, nöroşirürji, indeks

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INTRODUCTION

A thesis is a document resulting from personal research on a topic of interest that has a varying degree of research quality (1). Two purposes of theses are to contribute to the scientific literature and to equip the researchers with skills essential for the profession that involves lifelong learning (2). Producing a thesis for specialization in medicine is a legal obligation for residents training in any field of medicine to complete their training in Turkey. The skills that a resident is expected to gain during this process are to develop a hypothesis by performing a literature search, plan and conduct research to test this hypothesis, interpret the results, and conclude by synthesizing the literature and their findings (3,4). Since this process can be overwhelming for an inexperienced individual, each thesis is conducted under the mentorship of a senior colleague, ideally an academic staff.

Although the publication of a thesis in a peer-reviewed journal is not mandatory to complete a specialty training program, doing so adds further value to the thesis. Recently, bibliometric studies were conducted to assess the publication status of theses in scientific journals, as well as associated factors (2,3,5-19). The institutional factors (affiliation, location), study-related factors (design, subject), author-related factors (gender, publication count, current academic title, and workplace), mentor-related factors (academic title), the interval from completion of the thesis to publication, and the journal index were among the factors that were investigated (5,6,8,10,13). However, most of them were descriptive and the remaining ones rarely went beyond univariate analysis. To the best of our knowledge, there were two bibliometric studies regarding specialty theses in neurosurgery in Turkey. Öğrenci et al. (15) performed a descriptive study regarding theses published in SCI/SCI-E indexed journals. The more recent study by Sarica et al. (7) has focused on the quality of the published journals and the academic activity of authors by looking into citations received, the impact factor of the journals, and the number of intraresidency publications. They didn't look into the differences between published and unpublished theses.

In this study, we performed a bibliometric analysis of recently completed neurosurgery specialty theses and assess the association of factors with the publication of theses in international peer-reviewed journals.

METHODS

Since no animal or humans were involved in the study, and a database search was conducted at publicly accessible websites, formal ethics approval was not required. The study was conducted in accordance with the Helsinki Declaration and the terms and conditions of the National Thesis Center of the Higher Education Council.

Between June 6-12, 2022, specialty theses for neurosurgery were searched in the online archive of the National Thesis Center of Higher Education Council (https://tez.yok.gov.tr/UlusalTezMerkezi). The search terms and fields that were used for this study are shown in Figure 1. Theses in the field of neurosurgery that were completed between 2015 and 2019 were included in this study. The theses carried out in disciplines other than neurosurgery were excluded from the study. The thesis title, study design, study subject, authors' name, institution's name, mentor's name, mentor's academic title, and publication year of the thesis were collected from the database. In theses with double mentors, the mentor that was listed first was taken into consideration.

A further search was conducted in the Scopus database (https://www.scopus.com; Elsevier, Amsterdam, Netherlands) to determine the total publication count and h-index of both the authors and mentors. Also, publications by authors in the Scopus database were browsed through individually to find a publication derived from the thesis. Finally, whether the authors have made any publications as the first author (excluding the ones derived from the thesis) was determined.

Institutions were categorized into university hospitals and training and research hospitals (UH and TRH, respectively). The academic title of the mentors was categorized into no title, assistant professor, associate professor, and professor.

Theses were categorized into two main groups based on study design, clinical studies, and experimental studies. For

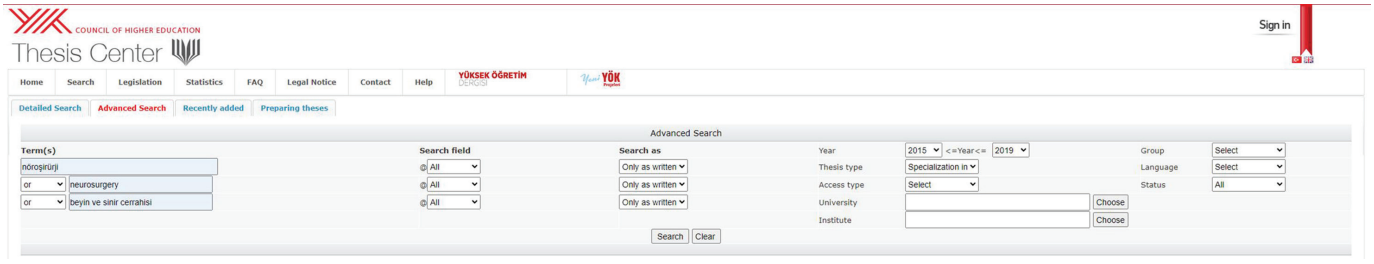

Figure 1. Search criteria used the online archive of the National Thesis Center of Higher Education Council

descriptive purposes, clinical studies were further divided into retrospective and prospective, whereas experimental studies were divided into the animal, cadaver, embryo, cell, and biomechanical studies.

The subject of the studies was assessed for univariate analysis only. Since there is not a universally accepted formal categorization for subspecialties of neurosurgery, the subjects were grouped based on education and training groups of the Turkish Neurosurgical Society (20). The subject topics were pediatric neurosurgery, spine and peripheral nerves, neurooncology, stereotactic functional pain and epilepsy (SFP&E), neurovascular surgery, surgical neuroanatomy, and miscellaneous.

Statistical Analysis

Statistical analyses were performed using SPSS 25.0 (IBM Corp, Chicago, USA) software. Descriptive statistics were expressed as median (minimum-maximum) for continuous variables, and observation number (%) for nominal variables. Normality analysis of continuous variables was assessed by the Kolmogorov-Smirnov test. Mann-Whitney U test was used to evaluate the statistically significant difference between groups in terms of continuous variables. The difference between nominal variables was analyzed by chi-square and Fisher-Freeman Halton Exact test. Logistic regression analysis was performed to identify factors that were associated with publication in the Scopus indexed journals. Odds ratio OR, 95% confidence interval and P values were determined for each variable. $P<0.05$ is regarded as statistically significant.

RESULTS

Two hundred and sixty-one theses were included in this study. Seventy theses were published in Scopus indexed journals. The mean interval from completion of a thesis to publication was 2.83±1.38 years.

One hundred and eighty-three theses were completed by residents in UHs compared to 78 from TRHs. The rate of published theses didn't show a significant difference between the two types of institutions.

The overall number of clinical and experimental studies were 128 and 133, respectively. The rate of publications derived from experimental studies was significantly higher in univariate analysis ($p=0.009$).

Animal experiments were the most frequent type of experimental studies in both published and unpublished theses. They were also the most frequently conducted study type in all published theses. In clinical studies, retrospective studies constituted a major portion of unpublished theses. On the other hand, they were only slightly more than prospective studies among published theses (18.6% vs 17.1%, respectively).

The most frequent topic both in the published and unpublished theses were spinal and peripheral nerves. This was followed by neurovascular surgery, neurooncology, and surgical neuroanatomy in unpublished theses and by neurooncology, neurovascular surgery, and SFP&E in published theses. Although the published and unpublished theses showed different trends in terms of study topics, this was not significant ($p=0.063$). The highest published/unpublished theses ratio belonged to the SFP&E (8/6) category, while the lowest ratio was observed in pediatric neurosurgery (3/13). Despite a high number of studies, the spine and peripheral nerve category also had one of the lowest published/unpublished ratios (17/69).

The author-related factors showed a significant difference between published and unpublished theses. The publication count of authors was significantly higher in published theses compared with unpublished ones. Similarly, the h-index of authors with published theses was significantly higher than those without. Finally, a significantly higher portion of the authors with a published thesis had at least one other article where they were the first author (60.0% and 15.7%, respectively).

Similar to authors, mentors of authors with published theses had a significantly higher number of published articles in Scopus indexed journals. On the other hand, the h-index and academic title of the mentors didn't show any significant difference between published and unpublished theses.

The demographic data regarding published and unpublished theses are summarized in Table 1 alongside the results of the univariate analysis.

The parameters that differed significantly between published and unpublished articles (publication count of the author, h-index of the author, publication count of the mentor, presence of first author publication, study design) were included in the logistic regression analysis. The publication count of the author and the presence of first-author articles were independently associated with the publication of theses (Table 2).

DISCUSSION

As every research, the thesis research generates knowledge and is expected to contribute to the literature. Although theses are considered scientific documents, they lack the potential to spread the knowledge they generated since they are usually limited to the university libraries

Table 1. Descriptive statistics and univariate analysis for evaluated factors in terms of publication status

	Not published in Scopus indexed journals (n=191)	Published in Scopus indexed journals (n=70)	p-value
Publication count [author] (median; range)	1 (0-49)	6 (1-46)	<0.001*
h-index [author] (median; range)	1 (0-11)	2 (0-9)	<0.001*
First-author article (n, %)	30 (15.7%)	42 (60.0%)	<0.001*
Year of the thesis			
2015	26 (13.6%)	14 (20.0%)	0.356
2016	31 (16.2%)	16 (22.9%)	
2017	52 (27.2%)	13 (18.6%)	
2018	43 (22.5%)	14 (20.0%)	
2019	39 (20.4%)	13 (18.6%)	
Publication count [mentor] (median; range)	40 (6-195)	51.5 (8-140)	0.027*
h-index [mentor] (median; range)	11 (3-28)	12.5 (3-25)	0.182
Institution (UH:TRH) (n)	132:59	51:19	0.665
Academic title			
No title (n, %)	10 (5.2%)	3 (4.3%)	0.630
Assistant professor (n, %)	30 (15.7%)	8 (11.4%)	
Associate professor (n, %)	69 (36.1%)	31 (44.3%)	
Professor (n, %)	82 (42.9%)	28 (40.0%)	
Study design			
Clinical	103 (53.9%)	25 (35.7%)	0.009*
Retrospective	79 (41.4%)	13 (18.6%)	
Prospective	24 (12.6%)	12 (17.1%)	
Experimental	88 (46.1%)	45 (64.3%)	
Animal	56 (29.3%)	36 (51.4%)	
Cadaver	25 (13.1%)	6 (8.6%)	
Biomechanical	4 (2.1%)	0 (0.0%)	
Embryo	2 (1.0%)	0 (0.0%)	
Cell	1 (0.5%)	3 (4.3%)	
Topic			
Spine and peripheral nerve	69 (36.1%)	17 (24.3%)	0.063
Neurooncology	25 (13.1%)	12 (17.1%)	
Neurovascular surgery	30 (15.7%)	10 (14.3%)	
SFP&E	6 (3.1%)	8 (11.4%)	
Surgical neuroanatomy	24 (12.6%)	6 (8.6%)	
Pediatric neurosurgery	13 (6.8%)	3 (4.3%)	
Miscellaneous	24 (12.6%)	14 (20.0%)	
Publishing time (years) (mean ± SD)	-	2.83+1.38	

*Statistically significant. SD: Standard deviation, SFP&E: Stereotactic functional pain and epilepsy, TRH: Training and research hospital, UH: University hospital

Table 2. Logistic regression analysis of factors associated with theses' publication status in Scopus indexed journals

Model	Odds ratio (OR)	95% Confidence interval for OR		p-value
		Minimum	Maximum	
Publication count [author]	1.127	1.013	1.253	0.027*
h-index [author]	0.981	0.691	1.393	0.914
Publication count [mentor]	0.999	0.988	1.010	0.800
First-author article	3.045	1.389	6.675	0.005*
Study design	0.618	0.320	1.192	0.113
Constant	0.180	-	-	0.000

*Statistically significant

(3). The preferred mode of spreading this knowledge and contributing to literature is through publication in a scientific journal (4). So, since one of the purposes of a thesis is contribution to the literature, an unpublished thesis can not be considered as fulfilled its purposes completely. Also, publishing a thesis -that is not mandatory in Turkey- has advantages for those who pursuit an academic career.

The publication rates of specialty theses were investigated in several medical fields in Turkey. This rate ranged from 10.2% to 49.7% (2,3,5-18). This might be due to the index used for database search, criteria used for search, or study period. Interestingly, Özgen et al. (19) found a much lower overall publication rate (6.2%, range: 0.9-13.04%) for specialty theses completed between 1980-2005. However, they reported an increased publication rate toward the end of the evaluated period (19). The higher rates reported in the recent studies might have resulted from an ongoing increase in people publishing their theses.

In this study, we found that 26.8% of neurosurgery theses carried out between 2015 and 2019 were published in scientific journals. This is lower than what Sarica and Sayman (7) found (37.9%) in their study that covered 2000-2017 era. Interestingly, Öğrenci et al. (15) found a much lower rate (18%) between 2004 and 2013. Although they searched for publications in SCI/SCI-E-indexed journals, they used Pubmed/Medline, Google Scholar, and unspecified search engines. Also, they used the title of the theses in their search. In this regard, it is possible some publications could have been missed by Öğrenci et al. (15) Another reason might be the ongoing increase in the publication rate of specialty theses, as discussed above. However, because Sarica and Sayman's (7) study also searched Scopus indexed journals but covered a much longer timespan (17 years compared to 5 years of current study) and found a higher overall rate, we can assume that publication rates of neurosurgery fluctuated during these years.

The mean publishing time in our study was similar to other studies conducted in Turkey that ranged between 2.72±1.51 and 3.83±2.98 years (2,5,7,8,10-14). It was found that the publishing time in journals indexed in SCI/SCI-E was similar to those that didn't (10,14).

In Turkey, residency training has been given both in UHs and TRHs. Most of the specialty theses in Turkey were conducted in UHs (2,6,8,12,17,21). UHs are autonomous, focus on education and research, whereas TRH serve under government and prioritize health services. In this context, it can be expected that theses completed in university hospitals would be published more frequently. However, two individual studies found that the type of institution has no association with the publication of thesis (6,8). Our data support these findings.

The study topic and design are the most crucial element for a thesis. It must be chosen according to the area of interest of the resident, as well as the capabilities of the person and institution, novelty of the subject, and time required to complete the study. Despite clinical studies made up most of the theses, Söğütdelen et al. (6) reported an OR of 4.68 for publication in favor of animal experiments. This trend exists in other fields of medicine as well (5,10). However, there are also reports that found no association with study designs and publication status (8,14). Although we found an association between study design and publication status, it didn't emerge as an independent factor in multivariate analysis. This may have resulted from residents that pursuit of an academic career purposefully chose to do animal experiments for the thesis. Animal studies have more potential to be published owing to the original information they provide (10,14).

Duracinsky et al. (22) reported several author-related features as a barrier to publications, such as workload, inproficiency in English, and low budget, which can both limit the study itself and open access publishing. However, there are also motivating factors. Publishing a thesis contributes to cumulative knowledge of science, which is a main motivating factor for a true scientific spirit. Second, the publication of a thesis is a step toward an academic career. Similarly, Sayek and Yorgancı (23) reported that people with academic career expectations have published more. The association of publication status of the theses with active academic career or pursuit was confirmed by other studies (6,8,10). Although studies used different criteria to assess authors' post gradual academic activity, the findings show

that it was associated with the publication of the theses. Our results also showed that the authors with a first-author article and a higher number of published articles more likely to publish their theses.

Most thesis were mentored by a professor in our study. This is in concordance with similar studies in Turkey (8,9,21,24,25). However, the relationship with the title of the mentor and publication of a thesis was rarely investigated. Erim and Petekkaya (8) found that theses mentored by assistant professors were published more frequently. This might be related to the academic expectancy of assistant professors being higher than associate professors and professors. Although we found a similar association with the total publication count of mentors, this was not confirmed by multivariate analysis.

Regardless, the majority of these thesis were not published. The suggested reasons for not publishing a thesis were proposed to be related to heavy work load, motivation, mentoring and support, institutional research tradition, out-of-date thesis subject, low scientific quality, foreign language insufficiency, high submission/publication fees, and publication bias for negative results (4,5,7,10,22,26,27). An unpublished thesis does not reach the scientific community and can be regarded as financial loss, waste of time, and human resources. Moreover, since the majority of these studies are performed on either humans or animals and these studies are supposed to contribute to literature, non-publishing of these studies brings up the purpose of the study for debate ethically.

This study carries a few potential limitations. There may be theses that were not uploaded to the database. We didn't included theses of the last 2 years as similar studies, but this might still not be sufficient to reach a definitive status for the publication of the evaluated theses (28). And the unpublished status for a thesis doesn't mean they were never submitted to a journal.

CONCLUSION

The publication rates of recent neurosurgical specialty theses are similar to other disciplines, but still low. The publication of theses in indexed journals is a sign of academic success -first- of the institution -and second- the country where the study was conducted. The most significant factor that is associated with the publication of a thesis is the author himself. A person who is in pursuit of an academic career tends to publish their work. With that said, there are still a significant number of theses that were not published. The reasons behind this situation should be examined and people should be encouraged to contribute to the scientific community by publishing their theses.

ETHICS

Ethics Committee Approval: The study involved no animal or human and conducted on open access databases. So, a formal ethics committee approval is not relevant.

Informed Consent: The study does not require patient consent.

Authorship Contributions

Concept: S.B., Design: S.B., İ.B., Data Collection or Processing: S.B., İ.B., Analysis or Interpretation: S.B., Literature Search: S.B., İ.B., Writing: S.B.

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

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Research

Can Factors Predicting Malignancy in Intratesticular Masses with Negative Tumor Markers Prevent Overtreatment?

Tümör Belirteçleri Negatif Olan İntratestiküler Kitlelerde Maligniteyi Öngörebilecek Faktörler Aşırı Tedaviyi Önleyebilir mi?

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ABSTRACT

Objective: There is a need for additional predictive factors for the malignant/benign differentiation to prevent overtreatment in intratesticular mass lesions with negative tumor markers. In this study, we evaluated the usability of systemic inflammatory markers, neutrophil-to-lymphocyte ratio (NLR), and tumor in the preoperative differentiation of benign and malignant intratesticular mass lesions.

Methods: The records of patients who underwent radical inguinal orchiectomy with a preliminary diagnosis of testicular tumor between August 2007 and September 2020 were retrospectively reviewed. Patients with a malignant specimen histopathology result after radical orchiectomy were classified as group 1, and those with a benign pathology result were classified as group 2. The demographic data, tumor diameters, preoperative systemic inflammatory markers, and NLRs were statistically compared between the two groups. NLR was calculated by dividing the neutrophil count by the lymphocyte count.

Results: The study included a total of 78 patients, of whom 47 (60.3%) were in group 1 and 31 (39.7%) were in group 2. The mean tumor sizes of groups 1 and 2 were 3.74±2.24 cm and 1.87±1.30 cm, respectively, being significantly higher in group 1 ($p<0.001$). For groups 1 and 2, the mean white blood cell (WBC) counts were determined as 8.60±2.23 and 7.54±2.02 μ/L, respectively; the mean neutrophil counts as 5.30±1.77 and 4.34±1.40 μ/L, respectively; the mean neutrophil ratios as 63.0±8.22 and 56.9±7.28%, respectively; the mean lymphocyte ratios as 26.2±6.69 and 31.9±6.05%, respectively; and the mean NLR values as 2.72±1.44 and 1.87±0.54, respectively. The mean WBC count, neutrophil count, neutrophil ratio, and NLR were significantly higher in group 1 ($p=0.037$, $p=0.014$, $p<0.001$, and $p=0.002$, respectively), and the mean lymphocyte ratio was significantly higher in group 2 ($p<0.001$). The analysis of the pathological results showed that malignancy correlated positively with tumor size, WBC count, neutrophil count, neutrophil ratio, and NLR, and a negative correlation with the lymphocyte ratio.

Conclusion: Tumor diameter, WBC count, neutrophil count, neutrophil ratio, lymphocyte ratio, and NLR can be used as predictive factors in the differentiation of benign-malignant intratesticular masses with negative testicular cancer markers before radical orchiectomy to prevent overtreatment. While the increased values of tumor diameter, WCB count, neutrophil count, neutrophil ratio, and NLR correlate with the possibility of malignancy, a decreased lymphocyte ratio can be evaluated in favor of malignancy.

Keywords: Testicular tumor, radical orchiectomy, tumor marker, systemic inflammatory markers

ÖZ

Amaç: Tümör belirteçleri negatif olan intratestiküler kitlesel lezyonlarda aşırı tedaviyi önlemek için malign/benign ayrımında ek ön görücü faktörlere ihtiyaç duyulmaktadır. Biz de bu çalışmamızda sistemik enflamatuvar belirteçlerin, nötrofil lenfosit oranının (NLO) ve lezyon boyutlarının intratestiküler kitlesel lezyonların preoperatif benign malign ayrımında kullanılabilirliğini değerlendirdik.

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ÖZ

Gereç ve Yöntem: Ağustos 2007 ile Eylül 2020 tarihleri arasında testis tümörü ön tanısı ile radikal inguinal orşiektomi yapılan hastaların kayıtları retrospektif olarak incelendi. Radikal orşiektomi sonrası örnek patolojisi histolojik olarak malign gelen hastalar grup 1, benign gelenler ise grup 2 olarak sınıflandırıldı. Her iki grubun demografik verileri, tümör çapları, preoperatif sistemik enflamatuvar belirteçleri ve NLO'ları istatistiksel olarak analiz edildi. NLO nötrofil sayısının lenfosit sayısına bölünmesi ile tanımlandı.

Bulgular: Toplam 78 hasta çalışmaya dahil edildi. Bu hastaların 47'si (%60,3) grup 1'de, 31'i (%39,7) grup 2'deydi. Gruplar için ortalama lezyon boyutları sırasıyla 3,74±2,24 cm ve 1,87±1,30 cm olmak üzere grup 1'de anlamlı olarak fazla bulunmuştur (p≤0,001). Sırasıyla grup 1 ve grup 2 için ortalama beyaz kan hücresi (WBC) sayıları 8,60±2,23 µ/L ve 7,54±2,02 µ/L, ortalama nötrofil sayıları 5,30±1,77 µ/L ve 4,34±1,40 µ/L, ortalama nötrofil oranları %63,0±8,22 ve %56,9±7,28, ortalama lenfosit oranları %26,2±6,69 ve %31,9±6,05, ortalama NLO ise 2,72±1,44 ve 1,87±0,54 idi. Ortalama WBC sayıları, nötrofil sayıları, nötrofil oranları ve NLO değerleri grup 1'de anlamlı yüksek bulundu (p=0,037, p=0,014, p<0,001, p=0,002). Ortalama lenfosit oranları ise grup 2'de anlamlı olarak yüksek bulundu (p<0,001). Patolojik değerlendirme sonucunun malign saptanması tümör boyutu, WBC sayısı, nötrofil sayısı, nötrofil oranları ve NLO ile pozitif korelasyon, lenfosit oranları ile negatif korelasyon gösterdi.

Sonuç: Testis kanseri belirteçleri negatif olan intratestiküler kitlelerin radikal orşiektomi öncesi benign-malign ayrımında aşırı tedaviden kaçınmak için tümör çapı, WBC sayısı, nötrofil sayısı, nötrofil oranları, lenfosit oranları ve NLO ön görücü faktör olarak kullanılabilir. Tümör çapı, WBC sayısı, nötrofil sayısı, nötrofil oranları ve NLO artışı malignite olma ihtimali ile korelasyon gösterirken, lenfosit oranlarının azalması ise yine malignite lehine değerlendirilebilir.

Anahtar Kelimeler: Testis tümörü, radikal orşiektomi, tümör belirteci, sistemik enflamatuvar belirteçler

INTRODUCTION

Although testicular cancer accounts for less than 1% of all tumors in men, it is the most common solid tumor in those aged 20 to 34 years, with a steadily increasing global incidence over the last few decades (1). The standard initial treatment of testicular tumors is radical orchiectomy. However, it is considered that fertility may be affected after orchiectomy in these patients, and thus, sperm banking is recommended before the operation (2). Another factor to considered is the negative psychological effects of orchiectomy on the patient. Therefore, many studies emphasize that patients should receive counseling on testicular prosthesis insertion before and after orchiectomy (3). For all these reasons, a correct diagnosis of testicular cancer is critical. For this purpose, scrotal ultrasonography (USG) and serum tumor markers [human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH)] are used (4). However, although 90% of testicular cancers are histologically germ cell tumors (5), these markers are expressed in <60% of cases (6). Which may result in unnecessary radical orchiectomy due to misdiagnosis. Therefore, particularly in intratesticular mass lesions with negative tumor markers, there is a need for additional predictive factors to predict malignant-benign differentiation to prevent overtreatment. Some studies have evaluated the relationship of testicular tumors with systemic inflammatory markers examined in routine peripheral blood count analysis, particularly the neutrophil-to-lymphocyte ratio (NLR) (7-9). However, none of these studies evaluated whether systemic inflammatory markers and NLR could be used in the prediction of the benign/malignant differentiation before orchiectomy in intratesticular masses with negative tumor markers. In the current study, we evaluated the usability of systemic inflammatory markers, NLR, and lesion size in the preoperative differentiation of benign and malignant intratesticular mass lesions.

METHODS

After obtaining approval from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (decision no: 2022-03-06, date: 07.02.2022) and written consent from the patients, we retrospectively reviewed the records of all patients who underwent radical inguinal orchiectomy with a preliminary diagnosis of testicular tumor between August 2007 and September 2020. The diagnosis of the patients and lesion size determination was undertaken using preoperative scrotal color Doppler USG and additionally by the magnetic resonance imaging of the scrotum in some cases. Patients with elevated testicular tumor markers, paratesticular lesions, metastases in relevant screening, single testis, another active infective focus, chronic inflammatory disease, known hematological pathologies, and incomplete pre-orchiectomy data related to tumor markers and hematological parameters were excluded from the study. Patients with histologically malignant pathologies after radical orchiectomy were classified as group 1, and those with benign lesions were classified as group 2. The patients' demographic data (age, gender, etc.), preoperative biochemical results, and histopathological results of orchiectomy material were obtained from the hospital database. Biochemical tests included tumor markers (HCG, AFP, and LDH) and complete blood count (CBC) parameters.

Additionally, NLR was calculated by dividing the neutrophil count by the lymphocyte count.

Statistical Analysis

Categorical variables were given as numbers and percentages, and continuous variables as mean and standard deviation. The normality of the distribution of continuous variables was evaluated with the Shapiro-Wilk test. The mean values of two normally distributed independent groups were compared with Student's t-test, and those of two non-normally distributed groups were compared using the Mann-Whitney U test. The percentage of categorical variables was compared with the Pearson chi-square test, and the cut-off values for malignancy were determined using the receiver operating characteristics (ROC) curve analysis. The correlation between malignancy and tumor size and hematological parameters was tested using the sperm correlation analysis. The results were considered statistically significant at $p<0.05$.

RESULTS

The study included a total of 78 patients with testicular tumor markers (HCG, AFP, and LDH) within normal limits who underwent radical inguinal orchiectomy with a preliminary diagnosis of testicular tumor. The demographic data and laboratory characteristics of the patients are shown in Table 1. According to postoperative mass specimen histopathology, 47 (60.3%) patients were in the malignant group (group 1) and 31 (39.7%) were in the benign group (group 2). The mean age of the patients significantly differed between the groups, being determined as 35±9.8 years for group 1 and 44.4±18.5 years for group 2 (p=0.046). There was no significant difference between the two groups in relation to the laterality and preoperative diagnostic imaging methods used (Table 2). The mean lesion size was 3.74±2.24 cm in group 1 and 1.87±1.30 cm in group 2, indicating a significantly higher value for the former (p<0.001). Of the patients with malignant histopathology, 37 (79%) had seminoma, five (11%) had Leydig cell tumors, two (4%) had mixed germ cell tumors, two (4%) had embryonal carcinomas, and one (2%) had a yolk sac tumor. Of the patients with benign histopathology, twelve (39%) had fibrotic granulation, three (10%) had adenomatoid tumors, three (10%) had nodular Leydig cell hyperplasia, one (3%) had angyomixoma, one (3%) had hemorrhagic infarct, two (6%) had interstitial congestion, two (6%) had interstitial hyalinization, four (13%) had seminiferous tubular atrophy, two (6%) had intraparenchymal hemorrhage, one (3%) had leiomyoma. There was no significant difference between the groups in terms of testicular tumor markers. For groups 1 and 2, the mean white blood cell (WBC) counts were determined as 8.60±2.23 and 7.54±2.02 μ/L, respectively; the mean neutrophil counts as 5.30±1.77 and 4.34±1.40 μ/L, respectively, the mean neutrophil ratios as 63.0±8.22 and 56.9±7.28%, respectively; the mean lymphocyte ratios as 26.2±6.69 and 31.9±6.05%, respectively; and the mean NLR values as 2.72±1.44 and 1.87±0.54, respectively. The mean WBC count, neutrophil count, neutrophil ratio, and NLR were significantly higher in group 1 (p=0.037, p=0.014, p<0.001, and p=0.002, respectively), whereas the mean lymphocyte ratio was significantly higher in group 2 (p<0.001). There was no significant difference between the groups in terms of the remaining hematological parameters (Table 2).

The ROC curve analysis was performed to calculate the cut-off and area under the curve (AUC) values of the parameters predicting malignancy. The cut-off and AUC values were determined as 1.95 cm and 0.802, respectively for tumor size; 7.72 μ/L and 0.638, respectively for WBC; 5.32 μ/L and 0.649, respectively for neutrophil count; 64.2% and 0.686, respectively for neutrophil ratio; 29.7% and 0.267, respectively, for lymphocyte ratio; and 2.72 and 0.707, respectively for NLR (Table 3 and Figure 1). The correlation analysis performed between a malignant pathological result and tumor size, WBC count, neutrophil count, neutrophil ratio, lymphocyte ratio, and NLR revealed that malignancy development correlated negative with the lymphocyte ratio and a positive correlation with the remaining parameters (Table 4).

DISCUSSION

The standard initial treatment of testicular tumors is radical orchiectomy (2). However, an unpredictable diagnosis may result in patients being more exposed to harmful effects on endogenous testosterone, fertility, and body image due to overtreatment (10). Therefore, many researchers have conducted studies on partial orchiectomy in testicular tumors (10,11). Studies on all testis-sparing procedures recently show the importance of an accurate diagnosis preoperatively (10,11). Negative tumor markers, which are used to support the diagnosis process, may make it difficult to differentiate between benign and malignant intratesticular mass lesions. Thus, there is a need for additional predictive factors that can predict the benign-malignant differentiation in this patient group.

Technological developments recently have improved the resolution of USG devices and increased the diagnosis of incidental testicular masses. Carmignani et al. (12) reported that non-palpable testicular lesions with a size of less than 2.5 cm on USG could be diagnosed incidentally, and 80%

Table 1. Demographic data and laboratory characteristics

Number of patients	78
Mean age ± SD, year	38.7±14.5
Laterality, n (%)	
Right (0)	48 (61.5)
Left (1)	30 (38.5)
Imaging method, n (%)	
1	31 (39.7)
2	47 (60.3)
Mean tumor diameter ± SD, cm	3.00±2.12
Mean WBC count ± SD, µ/L	8.18±2.20
Mean RBC count ± SD, 10^6 µ/L	5.17±0.71
Mean HGB count ± SD, g/dL	14.7±1.77
Mean HTC count ± SD, %	43.5±4.77
Mean PLT count ± SD, 10^3 µ/L	273±85.8
Mean MCV count ± SD, fL	84.9±5.58
Mean MCH count ± SD, pg	28.2±4.05
Mean MCHC count ± SD, g/dL	33.6±1.96
Mean RDW-CV count ± SD, %	13.1±1.49
Mean neutrophil count ± SD, µ/L	4.92±1.69
Mean lymphocyte count ± SD, µ/L	2.25±0.70
Mean eosinophil count ± SD, µ/L	0.16±0.14
Mean monocyte count ± SD, µ/L	0.61±0.20
Mean basophil count ± SD, µ/L	0.40±1.54
Mean neutrophil ratio ± SD, %	60.6±8.35
Mean lymphocyte ratio ± SD, %	28.5±6.99
Mean eosinophil ratio ± SD, %	2.37±1.70
Mean monocyte ratio ± SD, %	7.80±2.02
Mean basophil ratio ± SD, %	0.64±0.32
Mean MPV count ± SD, fL	9.62±1.26
Mean PCT ratio ± SD, %	0.26±0.09
Mean PDW-CV count ± SD, %	14.3±3.49
Mean NLR ± SD	2.38±1.23
Mean PLR ± SD	134±66.5
Mean LMR ± SD	3.88±1.38
Mean preop AFP ± SD, ng/mL	2.91±1.56
Mean preop bHCG ± SD, mIU/mL	0.66±0.84
Mean preop LDH ± SD, U/L	197±30.6

SD: Standard deviation, WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, HTC: Hematocrit, PLT: Platelet, MCH: Mean corpuscular hemoglobin, MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, LMR: Lymphocyte to monocyte ratio, AFP: Alfa-fetoprotein, bHCG: Human chorionic gonadotropin, LHD: Lactate dehydrogenase

of these lesions had a benign histology result. In another study by Guner and Tonyalı (13), it should be considered that the lesions may be highly benign, especially in patients aged between 15-34 years, who are small, non-palpable, do not cause elevation in serum tumor markers, and where testicular tumors are common, and if necessary, testicular sparing surgery should be planned. In the current study, we evaluated whether tumor size could be a predictive parameter in the differentiation of benign and malignant lesions. We determined that the mean tumor size was 3.74±2.24 cm in the malignant group and 1.87±1.30 cm in the benign group, being significantly higher in the former ($p<0.001$). Similarly, the increase in tumor size showed a significant correlation with malignancy, with the cut-off value being calculated as 1.95 cm. Thus, our results contribute to the current literature by demonstrating that tumor size can be a predictive parameter in the differentiation of benign and malignant lesions.

Studies conducted in the past decade suggest that immune and inflammatory cells contribute to angiogenesis to facilitate the survival and even proliferation of cancer cells during tumor development stages, and they produce various cytokines and chemokines for this purpose (14). In particular, the excessive release of interleukin (IL)-8 from tumor cells has a chemoattractant effect on neutrophils. It is known that IL-8 not only contributes to angiogenesis but also facilitates the growth and migration of tumoral cells with the enzymes secreted by neutrophils (15). Lymphocytes, on the other hand, are known as a surrogate for host cell-mediated immunity, playing a role in host defense against malignancy. In a patient with cancer, the lymphocyte count can be reduced by lymphocytic cytokines secreted by the tumor. This has been proven by the *in vivo* demonstration of ligands such as FasL and tumor necrosis factor β produced for cancer-induced lymphocyte apoptosis in cancer cases (16). All this evidence suggests that systemic inflammatory markers that can be determined in a simple CBC analysis can support the preliminary diagnosis of many malignancies and provide preliminary information about their prognosis.

Some studies have stated that systemic inflammatory markers and NLR may be important markers in predicting the prognosis of urological malignancies (17). Recently, many researchers have presented an association between testicular cancer and systemic inflammatory markers and NLR (7-9). Gokcen et al. (7) compared peripheral blood count and NLR between 39 patients that underwent radical orchiectomy for testicular cancer and 82 patients that underwent varicocelectomy and reported that the WBC count of the testicular cancer group was significantly higher

Table 2. Comparison of patient characteristic according to the pathology results

Variables	Malignant	Benign	p-value
Number of patients	47	31	
Mean age ± SD, year	35.0±9.82	44.4±18.5	0.046**
Laterality, n (%)			
Right (0)	30 (63.8)	18 (58.1)	0.609#
Left (1)	17 (36.2)	13 (41.9)	
Imaging method, n (%)			
1	18 (38.3)	13 (41.9)	0.748#
2	29 (61.7)	18 (58.1)	
Mean tumor diameter ± SD, (cm)	3.74±2.24	1.87±1.30	<0.001**
Mean WBC count ± SD, µ/L	8.60±2.23	7.54±2.02	0.037*
Mean RBC count ± SD, 10^6 µ/L	5.09±0.63	5.30±0.82	0.195*
Mean HGB count ± SD, g/dL	14.6±1.94	14.8±1.49	0.594*
Mean HTC count ± SD, %	43.3±5.31	43.8±3.69	0.648*
Mean PLT count ± SD, 10^3 µ/L	277±93.5	266±73.4	0.575*
Mean MCV count ± SD, fL	85.2±5.53	84.4±5.71	0.526*
Mean MCH count ± SD, pg	28.1±4.89	28.5±2.34	0.684*
Mean MCHC count ± SD, g/dL	33.7±1.54	33.4±2.49	0.573*
Mean RDW-CV count ± SD, %	13.2±1.59	12.8±1.29	0.155*
Mean neutrophil count ± SD, µ/L	5.30±1.77	4.34±1.40	0.014*
Mean lymphocyte count ± SD, µ/L	2.17±0.76	2.36±0.60	0.240*
Mean eosinophil count ± SD, µ/L	0.17±0.15	0.15±0.11	0.462*
Mean monocyte count ± SD, µ/L	0.61±0.22	0.62±0.19	0.977*
Mean basophil count ± SD, µ/L	0.49±1.71	0.26±1.25	0.521*
Mean neutrophil ratio ± SD, %	63.0±8.22	56.9±7.28	<0.001*
Mean lymphocyte ratio ± SD, %	26.2±6.69	31.9±6.05	<0.001*
Mean eosinophil ratio ± SD, %	2.50±1.91	2.18±1.32	0.410*
Mean monocyte ratio ± SD, %	7.52±2.20	8.21±1.68	0.135**
Mean basophil ratio ± SD, %	0.65±0.36	0.63±0.26	0.800*
Mean MPV count ± SD, fL	9.76±1.24	9.41±1.27	0.237*
Mean PCT ratio ± SD, %	0.27±0.10	0.25±0.08	0.277*
Mean PDW-CV count ± SD, %	13.8±3.35	15.0±3.63	0.146*
Mean NLR ± SD	2.72±1.44	1.87±0.54	0.002**
Mean PLR ± SD	145±78.9	116±36.1	0.143**
Mean LMR ± SD	3.80±1.58	4.01±1.00	0.524*
Mean preop AFP ± SD, ng/mL	2.91±1.65	2.91±1.45	0.988*
Mean preop bHCG ± SD, mIU/mL	0.74±0.99	0.52±0.55	0.267*
Mean preop LDH ± SD, U/L	198±31.1	197±30.2	0.921*

SD: Standard deviation, WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, HTC: Hematocrit, PLT: Platelet, MCH: Mean corpuscular hemoglobin, MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, LMR: Lymphocyte to monocyte ratio, AFP: Alfa-fetoprotein, bHCG: Human chorionic gonadotropin, LHD: Lactate dehydrogenase
*Independent-samples t-test
**Mann-Whitney U test
#Pearson chi-square test

(8.4±2.2 vs. 7.1±1.5). Similarly, in our study, WBC count was significantly higher in the malignant group, and its cut-off value was determined as 7.72 in the ROC analysis. In another study comparing the preoperative peripheral blood values between 36 patients with testicular cancer and 36 patients that underwent varicocelectomy, the authors reported that the neutrophil count and neutrophil ratio were significantly higher and the lymphocyte ratio was significantly lower in the testicular cancer group (8). Similarly, we observed that neutrophil count and neutrophil ratio were significantly higher in the malignant group, whereas lymphocyte ratio was significantly lower. We calculated the cut-off values of neutrophil count, neutrophil ratio, and lymphocyte ratio as 5.32, 64.2, and 29.7, respectively. In the literature, the mean NLR value in testicular cancer ranges from 2.37 to 3.18, and NLR is reported to be significantly higher in patients with localized testicular cancer compared to controls (8,9,18). Ilktac et al. (18) determined the mean NLR value of patients with localized testicular cancer as 2.78±1.84 before radical orchiectomy and 1.57±0.58 postoperatively, noting a significantly higher mean value in the preoperative period. In our study, the mean NLR value was 2.72±1.44, and it was significantly higher in the malignant group. A common goal of these studies was to determine the optimal cut-off value of NLR in testicular cancer (7,8). Gokcen et al. (7) determined the cut-off value of NLR for testicular cancer as 2.25, while another study determined the NLR cut-off value as 2.06 for testicular cancer (8). In our study, the NLR cut-off value was 2.72. Almost all the studies discussed in this paper evaluated the relationship of testicular cancer with systemic inflammatory markers and NLR, selecting controls from patients that underwent varicocelectomy due to another pathophysiology. In contrast, in our control group, we included patients that underwent orchiectomy with a preliminary diagnosis of testicular cancer but were found to have benign specimen pathology results. Thus, unlike the literature, all the patients included in our sample had negative testicular tumor markers. Therefore, we consider that the systemic inflammatory markers and NLR data

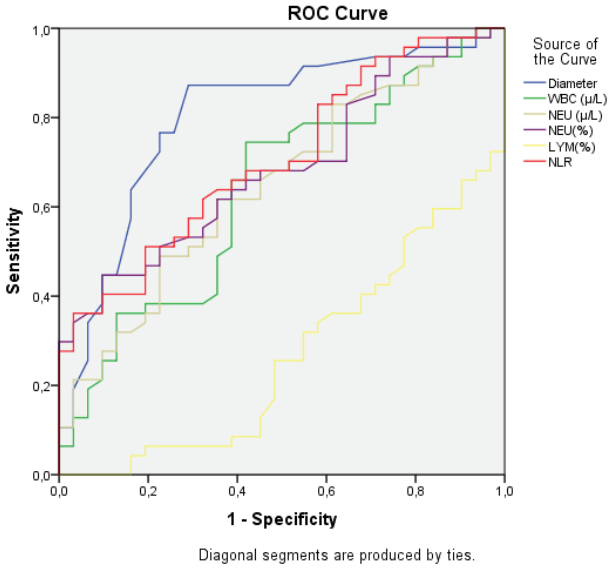

Figure 1. Receiver operating characteristic (ROC) analysis of the investigated parameters with their optimal cut-off values
ROC: Receiver operating characteristic, WBC: White blood cell, NEU: Neutrophil, LYM: Lymphocyte, NLR: Neutrophil-to-lymphocyte ratio

Table 3. ROC curve analysis results of the parameters predicting malignancy

	Cut-off value	Sensitivity-specificity	AUC	95% CI	p-value
Variables					
Tumor diameter	1.95	(87.2-71.0%)	0.802	0.698-0.906	<0.001
WBC count (µ/L)	7.72	(61.3-66.0%)	0.638	0.512-0.764	0.040
Neutrophil count (µ/L)	5.32	(48.9-77.4%)	0.649	0.526-0.772	0.026
Neutrophil ratio (%)	64.2	(44.7-90.3%)	0.686	0.570-0.802	0.006
Lymphocyte ratio (%)	29.7	(63.8-67.7%)	0.267	0.156-0.378	0.001
NLR	2.72	(36.2-96.8%)	0.707	0.593-0.821	0.002

WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, AUC: Area under the curve, CI: Confidence interval

Table 4. Correlation of malignancy with tumor diameter and hematological parameters

Spearman's rho		Diameter	WBC (µ/L)	Neu (µ/L)	Neu (%)	Lym (%)	NLR
Malignancy	CC	0.432	0.237	0.278	0.355	-0.401	0.337
	Sig. (2-tailed)	<0.001	0.037	0.014	0.001	<0.001	0.003

WBC: White blood cell, Neu: Neutrophil, Lym: Lymphocyte, NLR: Neutrophil-to-lymphocyte ratio

obtained from our study can provide a new perspective for the literature in terms of the differentiation of benign/malignant testicular masses with negative tumor markers before orchiectomy.

This study has certain limitations, such as the retrospective and single-center design. Therefore, our findings should be confirmed by prospective randomized studies.

CONCLUSION

Tumor diameter, WBC count, neutrophil count, neutrophil ratio, lymphocyte ratio, and NLR can be used as predictive factors in the differentiation of benign-malignant intratesticular masses with negative testicular cancer markers before radical orchiectomy to prevent overtreatment. While the increased values of tumor diameter, WBC count, neutrophil count, neutrophil ratio, and NLR correlate with the possibility of malignancy, a decreased lymphocyte ratio can be evaluated in favor of malignancy.

ETHICS

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (decision no: 2022-03-06, date: 07.02.2022).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Authorship Contributions

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

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Research

Comparison of COVID-GRAM, 4C Mortality, qSOFA, SIRS, NEWS, and MEWS in Predicting Mortality in COVID-19

COVİD-19 Hastalarında Mortaliteyi Tahmin Etmede COVID-GRAM, 4C Mortalite qSOFA, SIRS, NEWS ve MEWS'nin Karşılaştırılması

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ABSTRACT

Objective: Mortality prediction methods are still controversial about coronavirus disease-2019 (COVID-19) pneumonia. This study aimed to compare the efficacy of the the quick Sequential Organ Failure Assessment, systemic inflammatory response syndrome (SIRS), Modified Early Warning score (MEWS), National Early Warning score, 4C mortality, and COVID-GRAM critical illness risk score (COVID-GRAM), scoring systems in predicting 28-day mortality in adult patients with COVID-19.

Methods: This single-center, retrospective, observational cohort study included patients presenting to a pandemic hospital between November 2021 and December 2021. Inclusion criteria were patients aged 18 years or older, patients with positive reverse transcription-polymerase chain reaction test, and thoracic computed tomography imaging. The receiver operating characteristic analysis was performed to examine the diagnostic accuracy of the investigated scoring systems in predicting 28-day mortality. Statistical analyses were performed using the SPSS and MedCalc software packages. A p-value of <0.5 was considered statistically significant.

Results: The study was conducted in 846 patients. The median age of the patients included in the study was 49 (36-75) years, and the rate of male patients was 46.3% (n=392). The rate of pneumonia detection was 85.1% (n=720). The hospitalization rate was 49.6% (n=420), the admission rate to the intensive care unit was 7.4% (n=63), and the 28-day mortality rate was 5.7% (n=48). The highest area under the curve (AUC) values for 28-day mortality prediction was obtained from COVID-GRAM (AUC: 0.935) and 4C mortality (AUC: 0.922) scores, while the lowest AUC values were calculated in SIRS (AUC: 0.756) and MEWS (AUC: 0.805).

Conclusion: According to our results, COVID-GRAM may be the first-choice scoring system in the emergency department for predicting the 28-day mortality associated with COVID-19.

Keywords: COVID-19, scoring systems, COVID-GRAM, 4C mortality, qSOFA

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVİD-19) pnömonisi ile ilgili mortalite tahmin yöntemleri halen tartışmalıdır. Bu çalışmanın amacı, COVİD-19'lu erişkin hastalarda 28 günlük mortaliteyi tahmin etmede hızlı Sıralı Organ Yetmezliği değerlendirmesi, sistemik enflamatuvar yanıt sendromu (SIRS), Modifiye Erken Uyarı skoru (MEWS), Ulusal Erken Uyarı skoru, 4C mortalite ve COVID-GRAM kritik hastalık risk skoru (COVID-GRAM) skorlama sistemlerinin etkinliğini karşılaştırmaktır.

Gereç ve Yöntem: Bu tek merkezli, retrospektif, gözlemsel kohort çalışmasına Kasım 2021 ile Aralık 2021 arasında bir pandemi hastanesine başvuran hastalar dahil edildi. Dahil edilme kriterleri 18 yaş ve üstü hastalar, pozitif ters transkripsiyon-polimeraz zincir reaksiyonu testi ve torasik bilgisayarlı tomografi görüntülemesi olan hastalar idi. Araştırılan skorlama sistemlerinin 28 günlük mortaliteyi tahmin etmedeki tanısal doğruluğunu incelemek için alıcı işletim özelliği analizi yapıldı. İstatistiksel analizler SPSS ve MedCalc yazılım paketleri kullanılarak yapıldı. <0,5 p-değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışma 846 hasta ile gerçekleştirildi. Çalışmaya alınan hastaların ortanca yaşı 49 (36-75), erkek hastaların oranı ise %46,3 (n=392) idi. Pnömoni tespit oranı %85,1 (n=720) idi. Hastaneye yatış oranı %49,6 (n=420), yoğun bakıma yatış oranı %7,4 (n=63) ve 28 günlük mortalilte oranı %5,7 (n=48) idi. Yirmi sekiz günlük mortalite tahmini için en yüksek eğri altındaki alan (AUC) değerleri COVID-GRAM (AUC: 0,935) ve 4C mortalite (AUC: 0,922) skorlarından elde edilirken, en düşük AUC değerleri SIRS (AUC: 0,756) ve MEWS (AUC: 0,805) skorlarında hesaplanmıştır.

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ÖZ

Sonuç: Sonuçlarımıza göre COVID-GRAM, COVİD-19 ile ilişkili 28 günlük mortaliteyi tahmin etmek için acil serviste ilk tercih edilen skorlama sistemi olabilir.

Anahtar Kelimeler: COVİD-19, puanlama sistemleri, COVID-GRAM, 4C mortalite, qSOFA

INTRODUCTION

The worldwide effects of coronavirus disease-2019 (COVID-19) still continue in many variations and profoundly affect the entire healthcare system, including the habits of patients (1-4). Most COVID-19 patients recover with outpatient treatmen; however, some develop pneumonia and acute respiratory distress syndrome (ARDS) (5). The incidence of the critical disease has been found to be 5% in all COVID-19 patients and 15% in severe illness (6). On the other hand, as new waves continue to emerge in various regions of the globe, health systems are facing an increasing resource crisis (7). Predicting which patients will have a poor prognosis might aid in resource allocation. In the current COVID-19 phase, scoring systems have emerged as a critical tool for determining which patients need a more aggressive approach and which require a more moderate approach (8,9).

In patients with sepsis or septic shock, the Surviving Sepsis Campaign's 2021 guideline supports the use of systemic inflammatory response syndrome (SIRS), the quick Sequential Organ Failure Assessment (qSOFA), the National Early Warning score (NEWS), and the Modified Early Warning score (MEWS) (10). However, the 2020 COVID-19 guideline produced as part of the same campaign makes no proposal for a comparable COVID-19 scoring system (11). As a result, further study in this area is necessary. Despite the availability of several traditional and new scoring methods, their applicability in patients with COVID-19 has been debated (12). While only a few of these systems have been subjected to external validation, most have reported insufficient results in enough patients (12). COVID-GRAM is a scoring system established to identify patients with COVID-19 who need invasive mechanical ventilation in the intensive care unit (ICU) and to predict death (13). This scoring method considers ten distinct criteria and categorizes individuals as having a low, moderate, or high risk of developing a serious disease. Another scoring method, the 4C mortality score, was validated using data from 35,463 patients gathered from 260 hospitals in collaboration with the International Severe Acute Respiratory and Emerging Infections Consortium and the World Health Organization (WHO) Clinical Characterization Protocol (14). Numerous researches have shown the usefulness of both rating systems.

The purpose of this retrospective observational research was to compare the effectiveness of the qSOFA, SIRS, MEWS, and NEWS scoring systems, which are recommended in the sepsis guidelines, to the COVID-GRAM and 4C mortality scoring systems, which were designed particularly for COVID-19. Our secondary objective was to ascertain which of these scoring systems was superior to the others and to examine their practical applicability.

METHODS

The Ethical Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2021-23-26, date: 06.12.2021) and the Turkish Ministry of Health authorized this study. The research was planned as a retrospective, observational, cohort study at a single site.

Setting

This investigation was undertaken at Prof. Dr. Murat Dilmener Emergency Hospital, which was constructed by the Turkish Ministry of Health during the COVID-19 pandemic era. During the pandemic phase, the hospital takes around 110 ambulances per day and treats approximately 1,000 outpatients with COVID-19. The research period was from November 1, 2021, to December 5, 2021. Due to the retrospective nature of the study, the requirement for informed consent was waived; however, informed consent about the risks of COVID-19 and all treatment modalities (including cardiopulmonary resuscitation) was obtained from all patients or their varices at their first visit. Additionally, all individual information has been securely protected (by unlinking identifying information from the main dataset) and made available to researchers only. All the data were analyzed anonymously.

Protocol

The research comprised patients aged 18 years and older who had a positive real-time reverse transcription-polymerase chain reaction (RT-PCR) test on a nasopharyngeal swab sample and had thoracic computed tomography (CT).

The following exclusion criteria were used: a) unavailable or missing medical data, b) pregnancy, c) repeated hospitalizations within 15 days, and d) a prior lung infection or surgery, tuberculosis history, or imaging results consistent with COVID-19 pneumonia. All patients admitted to the pandemic hospital had the RT-PCR test. The participants were chosen using the process of thorough case analysis. The admission to the inpatient ward or ICU was determined using the Turkish Ministry of Health's COVID-19 Diagnosis and Treatment Guideline and the WHO's criteria for critical and severe disease. Thus, severe sickness was defined as the presence of severe clinical symptoms of pneumonia (fever, cough, dyspnea, and rapid breathing) in addition to one of the following criteria: respiration rate of more than 30 breaths per min, significant respiratory distress, or oxygen saturation lower than 90%. Critical illness was defined as the presence of ARDS or respiratory failure necessitating ventilation, sepsis, or septic shock.

The research gathered data from the hospital's automation system. Two separate doctors submitted data concurrently using a standard data form, and the results were compared using blinded selection. The research eliminated these patients with missing or erroneous data. For patient selection, the whole case analysis process was used. All metrics (blood pressure, vital signs, and CT results) were gathered from the patient's first visit to the emergency room. Scores were determined using the data form for each of the six distinct scoring systems examined in the research. Analyses were conducted in accordance with these computations. The duration of the disease was defined as the time period from the beginning of symptoms (fever, malaise, and cough) and presentation to the emergency room. On thoracic CT, pneumonia was diagnosed due to the presence of lung infiltration. The measurements and variables of the scoring systems are summarized in Table 1.

Statistical Analysis

Visual (histograms and probability graphs) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) approaches were used to determine the variables' compliance to the normal distribution. The premise of high normalcy was violated in terms of age, scoring system scores, vital parameters, and laboratory data. The Mann-Whitney U test was used to compare mortality across groups for numerical data and the chi-square test (or Fisher's Exact test, if applicable) for categorical data. The median and interquartile range (25^{th}-75^{th} percentile) values for numerical data were provided, while categorical data were expressed as frequencies and percentages. After computing the scores for each patient, the receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) values were calculated to determine the scoring systems' overall effectiveness in predicting 28-day mortality. The ideal threshold was determined for each score using the Youden index. In additionally, the sensitivity and specificity, positive and negative probability ratios, positive and negative predictive values, and accuracy of each score were calculated at the ideal threshold. The Hanley-McNeil test was used to examine the significance of the variations in the AUC values of the scores: Under the ROC curve, areas with a threshold Z ratio of 1.96 were judged distinct. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 26.0 (Armonk, New York), and MedCalc Statistical Software, Version 19.0.6 (MedCalc Software bvba, Ostend, Belgium; 2019). Statistical significance was defined as a p-value of.05 or less.

Outcomes

The primary outcome measure was each scoring system's diagnostic accuracy in predicting 28-day mortality. The secondary outcome was to compare the effectiveness of scoring systems in predicting 28-day mortality.

RESULTS

This study included data from 846 patients who met the inclusion and exclusion criteria. The median age of the patients included in the research was 49 (36-75) years, and 46.3% (n=392) of the patients were male. The median duration of sickness was 8 (6-10) days. The detection rate of pneumonia was 85.1% (n=720). The hospitalization rate was 49.6% (n=420), the admission rate to the ICU was 7.4% (n=63), and the 28-day mortality rate was 5.7% (n=48). Among hospitalized patients, the median length of stay was 9 (6-13) days.

The survival group had a median age of 47 (36-63) years, whereas the non-survivor group had a median age of 72 (65-89) years (Table 1). Among the vital signs, oxygen saturation ($p<0.001$), diastolic blood pressure ($p=0.030$), heart rate ($p=0.045$), and respiratory rate ($p<0.001$) were substantially different between the survivor and non-survivor group; however, neither systolic blood pressure or temperature was significantly different (Table 2). A statistically significant difference in white blood cell, neutrophil-lymphocyte ratio, urea, lactate dehydrogenase, direct bilirubin, and C-reactive protein levels was identified between the survivor and mortality groups. Table 2 includes information on the study population. Except for chronic kidney disease and malignancy, the mortality group had significantly higher rates of coronary artery disease ($p<0.001$), congestive heart failure, ($p=0.002$), chronic obstructive pulmonary

Table 1. Parameters used in the scoring systems

COVID-GRAM	4C mortality	qSOFA	SIRS	NEWS	MEWS
Age	Age >50 years	SBP ≤100 mmHg	HR >90	Heart rate	Heart rate
Dyspnea	RR >20 bpm	RR ≥22 bpm	RR >20 bpm or $PaCO_2$ <32 mmHg	RR	RR
Hemoptysis	SpO2 on room air	Altered mental status, GCS <15	WBC >12,000/mm^3, <4,000/mm^3, or >10% bands	SpO_2	SBP
Unconsciousness	GCS <15	Is this a COVID-19 patient?		Any Supplemental Oxygen	Temperature
X-ray abnormality	CRP >5 mg/dL			AVPU score	AVPU score
Number of comorbidities	BUN ≥19.6 mg/dL			Temperature	Is this a COVID-19 patient?
Cancer history				SBP	
NLR				Is this a COVID-19 patient?	
LDH					
Direct bilirubin					
Is this a COVID-19 patient?					

BUN: Blood urea nitrogen, CRP: C-reactive protein, GCS: Glasgow coma scales, MEWS: Modified Early Warning score, LDH: Lactate dehydrogenase, NEWS: National Early Warning score, NLR: Neutrophil-lymphocyte ratio, RR: Respiratory rate, SpO_2: Peripheral oxygen saturations, qSOFA: Quick Sequential Organ Failure Assessment, SIRS: Systemic inflammatory response syndrome, SBP: Systolic blood pressure, WBC: White blood cell

disease (p=0.002), chronic neurological disease (p=0.001), hypertension (p=0.001), and diabetes (p=0.009).

The ROC analysis was used to determine the scoring system's diagnostic accuracy in predicting 28-day mortality (Table 3, Figure 1). All scores have statistically significant AUC values (AUC >0.75). The COVID-GRAM (0.935) and 4C mortality (0.922) systems had the greatest AUC values for the 28-day mortality prediction, whereas SIRS (0.756) and MEWS had the lowest AUC values (0.805). The sensitivity, specificity, positive and negative probability ratios, positive and negative predictive values, and accuracy of ideal clinical thresholds are shown in Table 3, and comparisons of AUC values of scoring systems are presented in Table 4.

DISCUSSION

COVID-GRAM, 4C mortality, and NEWS were shown to be the most effective scoring systems for early prediction of death and ICU admission in COVID-19 (AUC >0.9). Additionally, qSOFA, MEWS, and SIRS were shown to be effective. While COVID-GRAM had the greatest AUC, NEWS showed the greatest sensitivity, and qSOFA demonstrated the greatest specificity. COVID-19 urgently requires the implementation of suitable grading methods for the identification of severely sick patients. COVID-GRAM is a ten-parameter scoring system (15). COVID-GRAM was shown to be a significant predictor of mortality and the requirement for intubation in validation trials [odds ratio: 4.16, 95% confidence interval (CI): 1.8-9.5] (15). COVID-GRAM seems to be a scoring system that may be used to forecast critically sick individuals considering the findings of our investigation (AUC: 0.935, 95% CI: 0.916-0.951). This scoring system, however, excludes indicators such as D-dimer ferritin, creatinine, and age that are used to predict death in COVID-19 (16). As a result, a new grading system based on these biomarkers may be more successful. On the other side, to use a scoring system such as COVID-GRAM, enough medical resources must be available. Additionally, the ideal score differs by area, because various resources are accessible in different regions of the globe during a pandemic. This poses a disadvantage in terms of COVID-broad GRAM's adoption. As a consequence, in order for the pandemic to cease, the disease's influence must reduce or disappear globally. Another successful scoring method that we discovered in our research is the 4C mortality scoring system, which comprises eight factors. It has previously been shown to be a good predictor of death in a derivation cohort of 35,463 patients (AUC: 0.79 and 95% CI: 0.78-0.79) and a validation cohort of 22,361 patients (AUC: 0.79 and 95% CI: 0.78-0.79). (AUC: 0.77, 95% CI: 0.76-0.77) (17). Additionally, this scoring system was shown to be a

Table 2. Descriptive statistics for patients' age, vital parameters, laboratory measurements, and critical illness prediction scores

	Survivor	Non-survivor	p-value
Age, median (25^{th}-75^{th})	47 (36-63)	72 (65-79)	<0.001
Vital signs, median (25^{th}-75^{th})			
Oxygen saturation	96 (94-98)	96 (94-98)	<0.001
Systolic blood pressure (mmHg)	132 (124-140)	128 (106-141)	0.063
Diastolic blood pressure (mmHg)	75 (66-85)	70 (60-81)	0.030
Heart rate (bpm)	89 (80-99)	96 (85-104)	0.045
Respiratory rate (bpm)	17 (15-18)	22 (18-24)	<0.001
Temperature (°C)	36.5 (36.3-36.7)	36.5 (36.4-36.7)	0.528
Laboratory measurements, median (IQR)			
White blood count ($\times 10^9$/L)	7.19 (5.20-9.92)	8.81 (5.94-15.09)	0.007
Neutrophil-lymphocyte ratio	3.12 (2.10-5.42)	9.88 (5.12-19.6)	<0.001
Urea (mg/dL)	28.4 (19.7-39.6)	48.7 (37.9-70.4)	<0.001
Lactate dehydrogenase, (U/L)	229 (179-305)	383 (290-505)	<0.001
Direct bilirubin (mg/dL)	0.15 (0.10-0.21)	0.21 (0.16-0.30)	<0.001
C-Reactive protein (mg/dL)	4.05 (2.05-6.71)	16.6 (14.7-18.5)	<0.001
Albumin (g/L)	41.7 (38.6-44.8)	34.7 (32.0-37.0)	<0.001
Critically illness prediction scores, median (25^{th}-75^{th})			
SIRS	1.0 (0.0-1.0)	2.0 (1.0-2.0)	<0.001
qSOFA	0.0 (0.0-0.0)	1.00 (0.5-1.0)	<0.001
NEWS	1.0 (1.0-3.0)	7.5 (6.5-10.5)	<0.001
MEWS	1.0 (1.0-2.0)	2.5 (2.0-4.0)	<0.001
4C mortality score	3.0 (1.0-6.0)	11.0 (9.0-13.5)	<0.001
COVID-GRAM	82 (61-105)	143 (126-168)	<0.001

COVID-GRAM: COVID-GRAM critical illness risk score, MEWS: Modified Early Warning score, NEWS: National Early Warning score, SIRS: Systemic inflammatory response syndrome, qSOFA: Quick Sequential Organ Failure Assessment

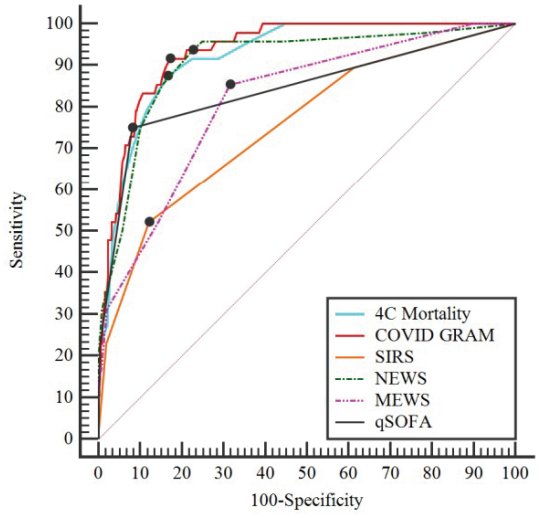

Figure 1. Area under the receiver operating curves of different scoring systems in prediction of mortality in COVID-19
COVID-GRAM: COVID-GRAM critical illness risk score, MEWS: Modified Early Warning score, NEWS: National Early Warning score, SIRS: Systemic inflammatory response syndrome, qSOFA: Quick Sequential Organ Failure Assessment, COVID-19: Coronavirus disease-2019

substantial predictor of death in our research (AUC: 0.922, 95% CI: 0.902-0.940). The variables employed in this scoring system include commonly accessible blood parameters that are easily determined, which contributes to the system's accessibility (17).

Clinicians have long used predictive scores to predict prognosis in patients with severe pneumonia, and research is ongoing (18-20). Sepsis caused by COVID-19 pneumonia has been included in the WHO's pandemic definition criteria for critical patients. The Surviving Sepsis Campaign's 2021 guideline shows a strong case of using SIRS, NEWS, or MEWS in patients with sepsis or septic shock rather than qSOFA (10). In 2020, this campaign produced a separate COVID-19 recommendation but made no reference to the effectiveness of any early warning system for this condition (11). SIRS involves blood parameters, but NEWS, MEWS, and qSOFA scores may be simply computed using Glasgow coma scale and vital signs readily available in practically any emergency room. On the other hand, due to the

Table 3. Sensitivities, specificities, negative and positive predictive values, positive and negative likelihood ratios for scoring systems for predicting 28-day mortality of COVID-19 patients

Scores	AUC (95% CI)	Cut-off values	Sens., %	Spec., %	PPV, %	NPV, %	LR+	LR-
COVID-GRAM	0.935 (0.916-0.951)	>112	91.67	82.83	24.3	99.4	5.34	0.10
4C mortality	0.922 (0.902-0.940)	>7	87.50	83.46	24.1	99.1	5.29	0.15
NEWS	0.908 (0.887-0.927)	>4	93.75	77.44	18.9	99.7	3.86	0.06
qSOFA	0.842 (0.816-0.866)	>0	75.00	91.85	35.6	98.4	9.21	0.27
MEWS	0.805 (0.777-0.831)	>1	83.33	68.42	13.7	98.6	2.64	0.24
SIRS	0.756 (0.725-0.784)	>1	52.08	87.84	20.5	96.8	4.28	0.55

AUC: Area under the curve, CI: Confidence interval, COVID-GRAM: COVID-GRAM critical illness risk score, MEWS: Modified Early Warning score, NEWS: National Early Warning score, NPV: Negative predictive value, SIRS: Systemic inflammatory response syndrome, qSOFA: Quick Sequential Organ Failure Assessment, Sens.: Sensitivity, Spec.: Specificity, PPV: Positive predictive value

Table 4. Comparison of the scores' superiority to one another

	COVID-GRAM	4C mortality	NEWS	qSOFA	MEWS
4C mortality	Z=0.908 p=0.364				
NEWS	Z=1.281 p=0.200	Z=0.601 p=0.548			
qSOFA	Z=0.008 p=2.652	Z=2.192 p=0.028	Z=2.199 p=0.028		
MEWS	Z=4.258 p<0.001	Z=3.574 p<0.001	Z=4.127 p<0.001	Z=1.107 p=0.268	
SIRS	Z=4.828 p<0.001	Z=4.298 p<0.001	Z=4.864 p<0.001	Z=2.021 p=0.043	Z=1.454 p=0.145

COVID-GRAM: COVID-GRAM critical illness risk score, MEWS: Modified Early Warning score, NEWS: National Early Warning score, SIRS: Systemic inflammatory response syndrome, qSOFA: Quick Sequential Organ Failure Assessment
The Hanley-McNeil test was used to evaluate if the differences in the AUCs of the scores were statistically significant: regions with a Z ratio greater than 1.96 under the receiver operating characteristic curve were deemed distinct

minimal number of factors and scorecards, the qSOFA score is the simplest to compute. All of these early warning systems were shown to be effective in predicting COVID-19-associated mortality in our research (AUC >0.75). NEWS was determined to be better than the other three scoring systems in specific. Additionally, whereas 4C mortality, COVID-GRAM, and SIRS all need laboratory testing, qSOFA, MEWS, and NEWS do not (21). Early diagnosis of severely sick patients is one of the most potent tools in doctors' arsenals when it comes to fighting pandemics. The optimal strategy would be to combine all existing scoring methods to create a single basic scoring system that produces findings with minimal variability and is useful in large population studies. COVID-19 is a pandemic virus with new variations emerging daily and presenting with various clinical symptoms and prognoses. As a result, no scoring system can be confidently stated to be optimal without knowing what the future holds. However, when we evaluated data from a pandemic hospital, we discovered that COVID-GRAM was the most effective scoring method for predicting COVID-19-related death. Thus, until the findings of novel variations or substantial clinical studies are acquired, this grading method may be used with confidence.

The study's retrospective design is a significant weakness. On the other hand, while we focused on scoring systems recommended by the Surviving Sepsis Campaign for patients with sepsis patients and those developed specifically for COVID-19, there are numerous additional parameters, including biomarkers and imaging findings, that are used to detect critical patients in COVID-19. Additionally, our findings reflect our region's shifting worldwide incidence of the illness throughout the continuing epidemic, as well as diverse patient features. Additionally since the information was derived from a pandemic hospital, it included patients with a moderate to bad prognosis, particularly because many patients with a poor prognosis were sent to our center from other hospitals. Finally, our findings may have been influenced by the removal of patients whose data could not

be obtained. The best scoring method will be determined via more thorough multicenter trials that integrate all scores used in COVID-19 for mortality and prognosis prediction.

CONCLUSION

According to our results, COVID-GRAM, when available, can be the first-choice scoring system in the effective prediction of mortality associated with COVID-19. However, in the presence of limited medical resources, NEWS would also provide reliable data for this purpose.

ETHICS

Ethics Committee Approval: The Ethical Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2021-23-26, date: 06.12.2021) and the Turkish Ministry of Health authorized this study.

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived; however, informed consent about the risks of COVID-19 and all treatment modalities (including cardiopulmonary resuscitation) was obtained from all patients or their varices at their first visit.

Authorship Contributions

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

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

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