ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 3 | Volume: 18 | Year: 2022

MEDICAL JOURNAL OF BAKIRKÖY

www.bakirkoytip.org

ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 3 | Volume: 18 | Year: 2022

MEDICAL JOURNAL OF BAKIRKÖY

Medical Journal of Bakırköy of is an official scientific Journal of University of Health Sciense Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (BMJ)

It is published quarterly as 4 issues every year (March, June, September, December).

Medical Journal of Bakirköy is an open Access, free and peer-reviewed journal and indexed in ESCI, EMBASE, Scopus, EBSCO and ULAKBİM TR Dizin.

Instructions for Authors and publication policy is available on our website.

www.bakirkoytip.org

Galenos Publishing House
Owner and Publisher
Derya Mor
Erkan Mor

Publication Coordinator
Burak Sever

Web Coordinators
Fuat Hocalar
Turgay Akpınar

Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülay Saday
Gülşah Özgül

Finance Coordinator
Sevinç Çakmak
Emre Kurtulmuş

Project Coordinators
Aybuke Ayvaz
Aysel Balta
Gamze Aksoy
Gülay Akın
Hatice Sever
Melike Eren
Nuran Akti
Özlem Çelik Çekil
Pınar Akpınar
Rabia Palazoğlu
Sümeyye Karadağ

Research&Development
Nihan Karamanlı

Digital Marketing Specialist
Ümit Topluoğlu

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25 **Fax:** +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Printing Date: September 2022
ISSN: 1305-9319 **E-ISSN:** 1305-9327
International scientific journal published quarterly.

Advisory Board

Advisory Board

Advisory Board

Advisory Board

Advisory Board

Advisory Board

Contents

Researches

266 **Approach of Physicians Working in Primary Healthcare Service to Asymptomatic Bacteriuria and Urinary Tract Infections**
Birinci Basamak Sağlık Hizmetlerinde Çalışan Hekimlerin Asemptomatik Bakteriüri ve İdrar Yolu Enfeksiyonlarına Yaklaşımı
Hakan Polat, Özlem Polat, Serdar Karadağ, İsmail Evren, Taner Kargı, Ali İhsan Taşçı; İstanbul, Turkey

273 **The Impact of Leukocytospermia and Semen Hyperviscosity on Sperm Parameters Among Men with Suspected Infertility**
İnfertilite Şüphesi Olan Erkeklerde Lökositopermi ve Semen Hiperviskozitesinin Sperm Parametreleri Üzerine Etkisi
Muhamet Afşin, Ayşe Feyda Nursal; Diyarbakır, Çorum, Turkey

278 **Does the "Risk-based Management Model" for Residual Disease in Patients with High-grade Cervical Intraepithelial Lesions Cause Overtreatment?**
Yüksek Dereceli Servikal İntraepitelyal Lezyonları Olan Hastalarda Rezidüel Hastalık için "Risk Bazlı Yönetim Modeli" Aşırı Tedaviye Neden Olur mu?
Mehmet Adıyeke, Suna Yıldırım Karaca, Sümeyye Ekmekci, Muzaffer Sancı; İzmir, Turkey

285 **Relationship Between Successful Antitachycardic Pacing Delivery and ICD Device Settings**
Başarılı Antitaşikardi Pacing Uyarımı ile ICD Cihaz Ayarları Arasındaki İlişki
Osman Pirhan, Abdülcelil Sait Ertuğrul; İstanbul, Turkey

290 **Comparison of the Use of Videolaryngoscopy and Direct Laryngoscopy Methods in Achieving Intubation Before Pediatric Cardiac Surgery**
Pediatrik Kalp Cerrahisinde Videolaringoskopi ile Direkt Laringoskopi Uygulamalarının Karşılaştırılması
Hatice Dilek Özcanoğlu, Funda Gümüş Özcan; İstanbul, Turkey

297 **Prognostic Significance of Soluble CD163 in Hospitalized Patients with COVID-19**
COVİD-19 ile Yatırılan Hastalarda Soluble CD163'ün Prognostik Önemi
Ahmet Nalbant, Tezcan Kaya, Selçuk Yaylacı, Deniz Çekiç, Kezban Süner, Cengiz Karacaer, Erdem Çokluk, Cahit Bilgin; Sakarya, Turkey

303 **Can Temporal Muscle Thickness Be a New Prognostic Factor for *De Novo* Glioblastoma?**
Temporal Kas Kalınlığı Yeni Tanı Glioblastoma için Prognostik Faktör Olabilir mi?
Elif Eda Özer, Meltem Kırlı Bölükbaş, Mustafa Orhan Nalbant, Gülşen Pınar Soydemir, Metin Figen, Esengül Koçak Uzel; İstanbul, Turkey

310 **Effect of the Adrenalectomy and Mineralocorticoid Receptor Antagonists on the Clinical and Biochemical Outcomes in Patients with Primary Aldosteronism: A Single-center Experience**
Primer Hiperaldosteronizmli Hastalarda Adrenalektomi ve Mineralokortikoid Reseptör Antagonisti Tedavisinin Klinik ve Biyokimyasal Sonuçlara Etkisi: Tek Merkez Deneyimi
Seda Turgut, Hamide Pişkinpaşa; İstanbul, Turkey

Contents

316 **Attitudes and Seropositivity Rates of Healthcare Workers for CoronaVac® During the COVID-19 Pandemic in a Pediatric Department**
Bir Pediatri Departmanında COVİD-19 Pandemisi Sırasında CoronaVac® Aşısı için Sağlık Çalışanlarının Tutumları ve Seropozitiflik Oranları
Nihal Akçay, Mehmet Emin Menentoğlu, Canan Baydemir, Esra Şevketoğlu; İstanbul, Kocaeli, Turkey

323 **Efficacy and Safety of Microscopic Bilateral Decompression with Unilateral Laminectomy in Geriatric Lumbar Spinal Stenosis Surgery**
Lomber Spinal Stenoz Cerrahisinde Unilateral Laminektomi ile Bilateral Dekompresyon Yaklaşımının Yaşlı Hastalarda Etkinlik ve Güvenilirliği
Doğan Güçlühan Güçlü, Duygu Dölen; İstanbul, Turkey

330 **Pediatric Lumbar Microdiscectomy**
Pediatrik Lomber Mikrodiskektomi
Doğan Güçlühan Güçlü; İstanbul, Turkey

336 **Does Growth Hormone Therapy Enlarge Pituitary Adenomas?**
Büyüme Hormonu Tedavisi Hipofiz Adenomlarını Büyütür mü?
Eda Çelebi Bitkin, Cengiz Kara, Serap Karaman, Murat Başaranoğlu, Adem Yokuş, Oğuz Tuncer; Van, İstanbul, Turkey

341 **A Prospective Analysis of the Association Between Sexual Dysfunction and Idiopathic Sensorineural Hearing Loss in Men**
Erkeklerde Cinsel İşlev Bozukluğu ile İdiyopatik Sensörinöral İşitme Kaybı Arasındaki İlişkinin Prospektif Bir Analizi
Doğan Çakan, Semih Uşaklıoğlu; İstanbul, Turkey

348 **Evaluation of Psychosocial Symptoms in Adolescents During the COVID-19 Pandemic in Turkey by Comparing Them with the Pre-pandemic Situation and Its Relationship with Quality of Life**
Türkiye'de COVİD-19 Pandemisi Döneminde Ergenlerde Psikososyal Belirtilerin Pandemi Öncesi Durumla Karşılaştırılması ve Yaşam Kalitesi ile İlişkisinin Değerlendirilmesi
Uğur Tekin; İstanbul, Turkey

357 **The Relationship Between Blood Transfusions and Mortality and Length of Stay in Patients Followed up with a Diagnosis of COVID-19 in Intensive Care Units**
COVID-19 Tanısıyla Yoğun Bakım Ünitelerinde Takipli Hastalarda Kan Transfüzyonlarının Mortalite ve Yoğun Bakımda Kalış Süreleri ile İlişkisi
Gülsen Keskin, Melis Sumak Hazır, Dilek Ünal, Jülide Ergil; Ankara, Turkey

365 **The Predictive Value of Systemic Immune Inflammation Index in Patients Hospitalized in the Intensive Care Unit**
Yoğun Bakım Ünitesinde Yatan Hastalarda Sistemik İmmün Enflamasyon İndeksinin Prediktif Değeri
Habip Yılmaz, Cemal Kazezoğlu, Asuman Gedikbaşı; İstanbul, Turkey

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:266-272
DOI: 10.4274/BMJ.galenos.2022.2022.4-18

Research

Approach of Physicians Working in Primary Healthcare Service to Asymptomatic Bacteriuria and Urinary Tract Infections

Birinci Basamak Sağlık Hizmetlerinde Çalışan Hekimlerin Asemptomatik Bakteriüri ve İdrar Yolu Enfeksiyonlarına Yaklaşımı

Hakan Polat[1], Özlem Polat[2], Serdar Karadağ[1], İsmail Evren[1], Taner Kargı[1], Ali İhsan Taşçı[1]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Urology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey

ABSTRACT

Objective: Asymptomatic bacteriuria (ASB) is often misdiagnosed as urinary tract infection. However, it does not require treatment. Although the guidelines recommend against the treatment of ASB with antibiotics, it has been reported that unnecessary antibiotic use is common, especially in outpatient centers. We evaluated the ASB approach in primary care physicians using an internet-based questionnaire.

Methods: In this study conducted between May-August 2021, family physicians working in family health centers in Istanbul and healthcare professionals work as family medicine specialists and residents in training-research hospitals were included. A form that was created to evaluate the descriptive features, urinalysis-urine culture conditions, and the treatments administered was used as a data collection tool.

Results: In this study, 436 family physicians were included. The findings showed that 91.3% (n=398) of the physicians gave treatment to patients who had positive urinalysis or urine culture and had no urinary symptoms. The rate of use of unnecessary treatment by physicians working in family health centers was significantly higher than that in hospitals. We observed that the most frequently used agent in the treatment is fosfomycin.

Conclusion: Most cases of overtreatment of ASB are based on the laboratory results rather than the clinical condition of the patients. The available evidence suggests that a combination of educational and organizational interventions would help improve the distinction between symptomatic urinary infection and ASB and adherence to evidence-based guidelines, and that ASB should be in a priority group for antimicrobial management programs.

Keywords: Asymptomatic bacteriuria, urinary tract infection, primary healthcare service

ÖZ

Amaç: Asemptomatik bakteriüri (ASB) genellikle tedavi gerektirmemesine rağmen idrar yolu enfeksiyonu olarak yanlış teşhis edilir. Kılavuzlar, ASB'nin antibiyotiklerle tedavisi aleyhine tavsiyede bulunmasına rağmen özellikle ayakta tedavi hizmeti verilen merkezlerde gereksiz antibiyotik kullanımının yaygın olduğunu bildirilmektedir. Çalışmamızda birinci basamak hekimlerinde ASB yaklaşımını internet tabanlı anket yoluyla değerlendirmeyi amaçladık.

Gereç ve Yöntem: Mayıs-Ağustos 2021 tarihleri arasında gerçekleştirilen araştırmada İstanbul ilinde aile sağlığı merkezlerinde görevli aile hekimleri ve eğitim-araştırma hastanelerinde aile hekimliği uzmanı ve asistanı olarak görev yapan sağlık çalışanları çalışma kapsamına alındı. Veri toplama aracı olarak; tanımlayıcı özellikler, idrar tahlili-idrar kültürü istenilen durumlar ve verilen tedavilerin değerlendirilmesi amacı ile oluşturulan bir form kullanıldı.

Bulgular: Çalışmaya toplam 436 aile hekimi dahil edilmiştir. Hekimlerin %91,3'ü (n=398) idrar tetkiki veya kültürü pozitif olup üriner semptomu olmayan hastalara tedavi verdiği saptanmıştır. Aile sağlığı merkezlerinde çalışan hekimlerin gereksiz tedavi uygulama oranı hastanelerde çalışanlara göre anlamlı derecede yüksekti. Tedavide en sık kullanılan ajanın fosfomisin olduğu görülmüştür.

Address for Correspondence: Hakan Polat, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Urology, Istanbul, Turkey
Phone: +90 212 414 71 71 E-mail: drhakanpolat@gmail.com ORCID ID: orcid.org/0000-0003-1525-1243

Cite as: Polat H, Polat Ö, Karadağ S, Evren İ, Kargı T, Taşçı Aİ. Approach of Physicians Working in Primary Healthcare Service to Asymptomatic Bacteriuria and Urinary Tract Infections. Med J Bakirkoy 2022;18:266-272

Received: 27.04.2022
Accepted: 23.06.2022

Sonuç: ASB'nin aşırı tedavisi olgularının çoğunun altında, hastanın klinik durumundan ziyade laboratuvar sonuçlarına göre yaklaşımda bulunulması yatmaktadır. Mevcut kanıtlar, semptomatik üriner enfeksiyon ile ASB arasındaki ayrımın iyileştirilmesinde ve kanıta dayalı kılavuzlara uyulmasında eğitici ve organizasyonel müdahalelerin bir kombinasyonunun faydalı olacağını ve ASB'nin antimikrobiyal yönetim programları için öncelikli grupta olması gerektiğini göstermektedir.

Anahtar Kelimeler: Asemptomatik bakteriüri, idrar yolu enfeksiyonu, birinci basamak sağlık hizmetleri

INTRODUCTION

Asymptomatic bacteriuria, defined as at least 10^5 CFU/mL uropathogen isolated in a sterile urine sample without symptoms of urinary tract infection (UTI), is a common condition in the community (1). Its incidence is estimated at 1%-5% in healthy premenopausal women, 4%-19% in healthy older women and men, 0.7%-27% in patients with diabetes mellitus, 2%-10% in pregnant women, 15%-50% in the older population in healthcare settings, and increases up to 23%-89% in patients with spinal cord injury (1). Asymptomatic bacteriuria (ASB) is often misdiagnosed as UTI, although it does not require treatment (2). Morbidity attributable to bacteriuria is defined only for pregnant women and patients scheduled for invasive urological procedures accompanied by mucosal trauma. Guidelines recommend against treating ASB with antibiotics because randomized trials demonstrated no clinical benefit (1). The harms of unnecessary antimicrobial use have been documented, including antibiotic-associated diarrhea, increased drug resistance to microorganisms, adverse drug reactions, and increased healthcare costs, respectively (3). Despite national guidelines recommending against antibiotic therapy for ASB, high-antibiotic treatment rates continue (4-7). Most of the antibiotics are prescribed within the scope of outpatient services (8,9). The literature shows that unnecessary broad-spectrum antibiotic use is common in outpatient centers (10).

Our study analyzes the approaches of primary care physicians to ASB through an internet-based questionnaire.

METHODS

Due to the lack of a central system and lack of documentation in our country, the diagnosis and treatment of diseases cannot be fully evaluated. Thus, we planned to evaluate the inappropriate treatment of UTI, which is common, by questionnaires of primary care physicians.

In this study conducted between May-August 2020, family physicians working in family health centers in Istanbul and health workers work as family medicine specialists and residents in training-research hospitals were included. According to the data of the medical chambers in Istanbul, there were 4,500 family physicians, and in our study, the number of cases to be taken to achieve 80% power at the α: 0.05 level was calculated as at least 354. A form that was created to evaluate the descriptive features, urinalysis-urine culture conditions and the treatments administered was used as a data collection tool. To determine the descriptive features, questions were asked to evaluate age, gender, workplace, tenure (year), in which cases urinalysis and urine culture were requested, and if so, what treatment was administered.

Data collection tools were prepared on Google forms and delivered to healthcare professionals online, and responses were collected in the same way. An invitation was sent to all participants using email on May 1, 2020, and the answers given until August 31, 2020, were recorded. All participants were informed before they started to fill out the form, and two options were presented on the informed consent page (yes/no). Only those who chose yes were included in this study. Due to the design of the questionnaire, all questions must be answered to ensure successful participation. In this study, 436 physicians who gave consent to participate in the study were included. It was accepted that no intervention that could disrupt the mucosal integrity of the urinary system would be planned in the primary care setting. The examinations and treatments performed on the asymptomatic patient, except for pregnancy, were evaluated as inappropriate.

Ethics statement: The methodology and questionnaire for this study were approved by the of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (decision no: 2021-04-15, date: 15.02.2021). The authors assert that all procedures contributing to this work comply with the ethical standards of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital and the Helsinki Decleration of 1975, as revised in 2008. The participants' consent to parcipate in the study was requested personally from each individual.

Statistical Analysis

The NCSS (Number Cruncher Statistical System) program was used for statistical analysis. Descriptive statistical methods (frequency, percentage) were used while evaluating the data. The Pearson chi-square test was used to compare qualitative data, Fisher's Exact test and Fisher-

Freeman-Halton test were used for categorical variables. Statistical significance was set as $p<0.05$.

RESULTS

This study was conducted with 436 family physicians; 55.5% (n=242) of them were females and 44.5% (n=194) males. 56% (n=244) of the physicians participating in this study were between the ages 25-35, 26.6% (n=116) were between the ages of 35-45, 14.7% (n=64) were between the ages of 45-55 and 2.8% (n=12) were from 55-65 years old.

It was observed that 34.4% (n=150) of the physicians participating in this study worked as resident family physicians, 22% (n=96) contracted family medicine specialists (CFMS), 34.9% (n=152) family physicians and 8.7% (n=38) were specialist family physicians.

It was observed that 59.6% (n=260) of the physicians were assigned to family health centers, 40.4% (n=176) to secondary and tertiary hospitals and 63.8% (n=278) of the physicians had 0-10 years of professional experience, 20.2% (n=88) had 10-20 years, 13.3% (n=58) had a 20-30-year period and 2.8% (n=12) had more than 30 years (Table 1).

They were asked, "in which situations would you like to have a urine test?" and the answers given by the physicians to the question were as follows: 85.3% (n=372) in case of pregnancy, 83% (n=362) when the systemic infection is suspected, 66.9% (n=292) in the presence of a urinary catheter, 29.8% (n=130) were in advanced age, 38.9% (n=170) from those with chronic disease and 91.7% (n=400) from patients with urinary symptoms.

Table 1. Distribution of descriptive features

Age	25-35 years	244 (56.0%)
	35-45 years	116 (26.6%)
	45-55 years	64 (14.7%)
	55-65 years	12 (2.8%)
Gender	Female	242 (55.5%)
	Male	194 (44.5%)
Type of physicians	Family medicine resident	150 (34.4%)
	CFMS	96 (22.0%)
	Family physicians	152 (34.9%)
	Family medicine specialist	38 (8.7%)
Work place	Family medicine center	260 (59.6%)
	Hospital	176 (40.4%)
Tenure (years)	0-10	278 (63.8%)
	10-20	88 (20.2%)
	20-30	58 (13.3%)
	>30	12 (2.8%)

CFMS: Contracted family medicine specialist

While 4.1% (n=18) of the physicians stated that they wanted routine urine culture and urinalysis, 95.9% (n=418) stated that they did not. Of the physicians who did not want a routine urine culture with urinalysis, 42.1% (n=176) stated that they wanted a routine urine culture from the patients with urinary symptoms, 32.5% (n=136) from those with chronic disease, 34% (n=142) from those who were pregnant, 70.3% (n=294) from those who had a urinary catheter, 18.2% (n=76) from those with advanced age and 23.4% (n=98) from those with other reasons.

While 46.8% (n=204) of the physicians stated that they wanted a culture from the patient who had urine examination (+) and had no urinary symptoms, 53.2% (n=232) stated that they did not want a culture. 91.3% (n=398) of the physicians stated that they gave treatment to patients who had positive urinalysis or culture (+) and had no urinary symptoms.

The findings showed that 79.9% (n=318) of the physicians used fosfomycin in the treatment, 44.7% (n=178) nitrofurantoin, 21.1% (n=84) quinolone, 13.6% (n=54) sulfonamide, 3.5% (n=14) penicillin, 21.1% (n=84) cephalosporin and 6% (n=24) other agents (Table 2).

There was no statistically significant difference between the distribution of the physicians' treatment-giving status according to age groups ($p>0.05$).

A statistically significant difference was found between the distribution of the physicians' treatment-giving status by gender. The rate of administering the necessary treatment by female physicians was significantly higher than that of male physicians ($p=0.001$; $p<0.01$).

A statistically significant difference was found between the distribution of the treatment status of the physicians according to their duties. The rate of administering the necessary treatment among specialist family physicians was significantly higher than in those with CFMS. Additionally, the rate of administering unnecessary treatment in those with CFMS and family physicians was significantly higher than in those with a family physician resident and family physician specialist ($p=0.001$; $p<0.01$).

A statistically significant difference was found between the distribution of the treatment status of the physicians according to their workplace. The rate of administering unnecessary treatment by physicians whose workplace was a family health center was significantly higher than that of physicians whose workplace was a hospital ($p=0.001$; $p<0.01$).

Table 2. Distribution of descriptive features

Urinalysis requests	Pregnancy	372 (85.3%)
	Suspicion of systemic infection (fever, chills, weakness, etc.)	362 (83%)
	Presence of urinary catheter	292 (66.9%)
	Elderly	130 (29.8%)
	Chronic diseases	170 (38.9%)
	Urinary symptoms	400 (91.7%)
Routine urine culture request with urinalysis	Yes	18 (4.1%)
	No	418 (95.9%)
Urine culture request cases of those who do not have a routine urine culture order with urinalysis	Urinary symptoms	176 (42.1%)
	Chronic disease	136 (32.5%)
	Pregnancy	142 (34.0%)
	Presence of urinary catheter	294 (70.3%)
	Elderly	76 (18.2%)
	Others	98 (23.4%)
Culture request from a patient who has a urinalysis (+) and has no urinary symptoms	Yes	204 (46.8%)
	No	232 (53.2%)
Treatment of patients with (+) urinalysis or culture and no urinary symptoms	No	38 (8.7%)
	Yes	398 (91.3%)
Antibiotics used in treatment	Fosfomycin	318 (79.9%)
	Nitrofurantoin	178 (44.7%)
	Quinolon	84 (21.1%)
	Sulfonamide	54 (13.6%)
	Penicillin	14 (3.5%)
	Cephalosporins	84 (21.1%)
	Others	24 (6.0%)

A statistically significant difference was found between the distribution of the treatment status of the physicians according to their tenure. The rate of providing necessary treatment for physicians with 20-30 years of tenure was significantly lower than those of physicians with a tenure of between 0 and 10 and 10-20 years ($p=0.001$; $p<0.01$) (Table 3).

DISCUSSION

The evaluation and improvement of antibiotic administration in outpatient treatment is a major issue. According to the data of the American Centers for Disease Control and Prevention, nearly 80% of antibiotic prescriptions are given in outpatient centers and it is reported that 30% of these prescriptions are unnecessary (11).

UTI is one of the most common infections for which antimicrobials are prescribed, and likewise, most patients prescribed antimicrobial agents do not require treatment (12). This is also true for ASB, which has proven to have a high prevalence, such as women, tuberculosis patients, and older people (13). The overtreatment of ASB may lead to many undesirable consequences, such as the disruption of intestinal flora, which increases the risk of *Clostridium difficile* infection, antibiotic resistance, and increased healthcare-related costs (5,14). Additionally, unnecessary antimicrobial therapy may lead to the development of symptomatic urinary infections by affecting low virulence strains that inhibit the development of uropathogens (15,16).

Guidelines report that diagnosis and treatment of ASB may be beneficial only in two groups of patients: pregnant women and patients scheduled for urological procedures at

Table 3. Comparisons according to treatment situations

		Treatment situations			
		Appropriate treatment (n=126)	Inappropriate treatment (n=276)	Treatment required but not prescribed (n=16)	
		n (%)	n (%)	n (%)	p
Age (years)	25-35	78 (32.5)	148 (61.7)	14 (5.8)	[a]0.076
	35-45	28 (25.9)	80 (74.1)	0 (0.0)	-
	45-55	18 (30.0)	40 (66.7)	2 (3.3)	-
	55-65	2 (20.0)	8 (80.0)	0 (0.0)	-
Gender	Female	82 (34.5)	140 (58.8)	16 (6.7)	[b]0.001**
	Male	44 (24.4)	136 (75.6)	0 (0.0)	
Type of physicians	Family medicine resident	48 (32.4)	88 (59.5)	12 (8.1)	[b]0.001**
	Contracted family medicine specialist	22 (24.4)	68 (75.6)	0 (0.0)	-
	Family physicians	40 (28.2)	102 (71.8)	0 (0.0)	-
	Family medicine specialist	16 (42.1)	18 (47.4)	4 (10.5)	-
Work place	Family medicine center	66 (26.8)	180 (73.2)	0 (0.0)	[b]0.001**
	Hospital	60 (34.9)	96 (55.8)	16 (9.3)	
Tenure (years)	0-10	86 (31.6)	172 (63.2)	14 (5.1)	[a]0.019*
	10-20	30 (37.5)	50 (62.5)	0 (0.0)	-
	20-30	8 (14.8)	44 (81.5)	2 (3.7)	-
	>30	2 (16.7)	10 (83.3)	0 (0.0)	-

[a]Fisher-Freeman-Halton test, [b]Pearson chi-square test, *p<0.05, **p<0.01

risk of mucosal disruption. Except for these patients, they strongly recommend that ASB not be screened or treated with antimicrobials (12).

Studies have shown that the prevalence of this inappropriate treatment ranges from 45% to 83% (17). The American Geriatrics Society and the American Foundation of Internal Medicine reported the unnecessary use of antimicrobials for ASB as one of the top five overused services in the "Choose Wisely Campaign" (18). In our study, the findings showed that the rate of inappropriate requests for urinalysis and culture was high. It was seen that high rates of urine examination were requested in cases where screening was not recommended, such as the presence of a urinary catheter, advanced age, and chronic disease. Given that 91.3% (n=398) of the physicians stated that they would administer treatment to patients who had (+) infection in urinalysis or culture and did not have urinary symptoms, inappropriate treatment is generally administered based on simple urine measurement strip results.

Urinalysis or microbiology cannot distinguish ASB from symptomatic UTI. Therefore, guidelines recommend the presence of two or more signs of UTI (such as dysuria, urgency urinate, frequent urination, flank pain or suprapubic pain) as the most accurate indication for diagnosis. Guidelines are against the use of urine dipstick tests and recommend urine culture only if there are signs and symptoms for prescribing antibiotics (19). The UK's National Institutes of Health and Clinical Excellence quality standard for elderly adults (QS260) also recommends diagnosing UTI with a complete clinical evaluation rather than urine test result due to varying accuracy (20).

If the urinalysis or culture is positive, it has been stated that 79.9% (n=318) of the participants used fosfomycin in the treatment, 44.7% (n=178) nitrofurantoin, 21.1% (n=84) cephalosporin, 21.1% (n=84) used quinolones, 13.6% (n=54) sulfonamides, 3.5% (n=14) penicillin and 6% (n=24) other agents. Fosfomycin and nitrofurantoin, which should be used as the first choice for treating uncomplicated UTI according to the guidelines, were also the most preferred agents in our study. Although appropriate agents are preferred regarding approach to the infection, it makes us think that the main problem here is the necessity of

diagnosing UTI and correcting the choice of treatment. Reasons, such as a lack of clinical distinction between ASB and UTI, presence of non-specific symptoms or comorbid conditions, excessive reliance on urinalysis with pyuria/nitrite positivity/high bacterial counts, are important in explaining overtreatment. In another survey of physicians, decision-making based solely on laboratory findings was the most common reason for overtreatment (4,21-23).

In the first step, ASB treatment can only be considered an appropriate approach for pregnant women. In the evaluation made regarding demographic characteristics, the rate of appropriate approach in primary care physicians with relatively high tenure was significantly lower than in other physicians. Additionally, the rate of appropriate treatment by family physician specialists was significantly higher than that with CFMS. Unnecessary treatment rates of those who worked in the CFMS program and family physicians were significantly higher than those of family medicine residents and specialists. In this respect, it is seen that continuing education and following the guidelines are important regarding an appropriate approach.

In a systematic review investigating the inappropriate management of patients with ASB, it was reported that most interventions aimed at minimizing the rate of improper treatment were successful and resulted in a 25%-80% decrease in improper treatment (5). Over-reliance on urinalysis appears to result in improper antibiotic prescribing for ASB. Interestingly, difficulties in reducing inappropriate treatment of ASB can be overcome, as relatively simple interventions (educational and/or organizational) reduce the rate of improper antimicrobial prescribing.

CONCLUSION

In conclusion, clinical practice in the approach to ASB appears to be in significant discord with evidence-based guidelines. Most cases of overtreatment of ASB underlie the approach based on laboratory results rather than the patient's clinical condition. The available evidence suggests that a combination of educational and organizational interventions would help improve the distinction between symptomatic urinary infection and ASB and adherence to evidence-based guidelines, and that ASB should be in a priority group for antimicrobial management programs.

ETHICS

Ethics Committee Approval: The methodology and questionnaire for this study were approved by the of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (decision no: 2021-04-15, date: 15.02.2021). The authors assert that all procedures contributing to this work comply with the ethical standards of Bakırköy Dr. Sadi Konuk Training and Research Hospital and the Helsinki Decleration of 1975, as revised in 2008.

Informed Consent: The participants' consent to parcipate in the study was requested personally from each individual.

Authorship Contributions

Concept: H.P., Ö.P., A.İ.T., Design: H.P., Ö.P., S.K., İ.E., A.İ.T., Data Collection or Processing: H.P., Ö.P., S.K., İ.E., T.K., Analysis or Interpretation: H.P., Ö.P., T.K., A.İ.T., Literature Search: H.P., S.K., İ.E., Writing: H.P., Ö.P., T.K., A.İ.T.

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

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

REFERENCES

1. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM; Infectious Diseases Society of America; American Society of Nephrology; American Geriatric Society. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 2005;40:643-54.
2. Fridkin S, Baggs J, Fagan R, Magill S, Pollack LA, Malpiedi P, et al. Vital signs: improving antibiotic use among hospitalized patients. MMWR Morb Mortal Wkly Rep 2014;63:194-200.
3. Christian KA, Ijaz K, Dowell SF, Chow CC, Chitale RA, Bresee JS, et al. What we are watching--five top global infectious disease threats, 2012: a perspective from CDC's Global Disease Detection Operations Center. Emerg Health Threats J 2013;6:20632.
4. Flokas ME, Andreatos N, Alevizakos M, Kalbasi A, Onur P, Mylonakis E. Inappropriate Management of Asymptomatic Patients With Positive Urine Cultures: A Systematic Review and Meta-analysis. Open Forum Infect Dis 2017;4:ofx207.
5. Chowdhury F, Sarkar K, Branche A, Kim J, Dwek P, Nangit A, et al. Preventing the inappropriate treatment of asymptomatic bacteriuria at a community teaching hospital. J Community Hosp Intern Med Perspect 2012;2.
6. Hartley S, Valley S, Kuhn L, Washer LL, Gandhi T, Meddings J, et al. Overtreatment of asymptomatic bacteriuria: identifying targets for improvement. Infect Control Hosp Epidemiol 2015;36:470-3.
7. Spivak ES, Burk M, Zhang R, Jones MM, Neuhauser MM, Goetz MB, et al. Management of Bacteriuria in Veterans Affairs Hospitals. Clin Infect Dis 2017;65:910-7.
8. Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Danziger LH. A national evaluation of antibiotic expenditures by healthcare setting in the United States, 2009. J Antimicrob Chemother 2013;68:715-8.
9. Schumock GT, Li EC, Suda KJ, Matusiak LM, Hunkler RJ, Vermeulen LC, Hoffman JM. National trends in prescription drug expenditures and projections for 2014. Am J Health Syst Pharm 2014;71:482-99.
10. Shapiro DJ, Hicks LA, Pavia AT, Hersh AL. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-09. J Antimicrob Chemother 2014;69:234-40.
11. Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA, File TM Jr, et al. Prevalence of Inappropriate Antibiotic

Prescriptions Among US Ambulatory Care Visits, 2010-2011. JAMA 2016;315:1864-73.

12. Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. Clin Infect Dis 2019;68:e83-110.
13. Nicolle LE. Asymptomatic bacteriuria: when to screen and when to treat. Infect Dis Clin North Am 2003;17:367-94.
14. Courjon J, Pulcini C, Cua E, Risso K, Guillouet F, Bernard E, et al. Antibiotics-related adverse events in the infectious diseases department of a French teaching hospital: a prospective study. Eur J Clin Microbiol Infect Dis 2013;32:1611-6.
15. Wullt B, Svanborg C. Deliberate Establishment of Asymptomatic Bacteriuria-A Novel Strategy to Prevent Recurrent UTI. Pathogens 2016;5:52.
16. Cai T, Mazzoli S, Mondaini N, Meacci F, Nesi G, D'Elia C, et al. The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: to treat or not to treat? Clin Infect Dis 2012;55:771-7.
17. van Horrik TM, Geerlings SE, Stalenhoef JE, van Nieuwkoop C, Saanen JB, Schneeberger C, et al. Deimplementation strategy to reduce overtreatment of asymptomatic bacteriuria: a study protocol for a stepped-wedge cluster randomised trial. BMJ Open 2021;11:e039085.
18. Choosing Wisely. An initiative of the ABIM foundation. Available at: http://www.choosingwisely.org/societies/american-geriatrics-society/. [Accessed 23.10.2021].
19. SIGN, 2012. Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary tract infection in adults. (SIGN Publ. no. 88) 1–52. Available at: https://www.sign.ac.uk/assets/sign88.pdf. [Accessed 13.11. 2021].
20. NICE, 2015. National Institute for Health and Care Excellence: Urinary tract infections in adults. Available at:https://www.nice.org.uk/guidance/qs90/chapter/quality-statement-1-Diagnosing-urinary-tract-infections-in-adults-aged-65-years-and-over. [Accessed 28.11.2021].
21. Drekonja DM, Gnadt C, Kuskowski MA, Johnson JR. Urine cultures among hospitalized veterans: casting too broad a net? Infect Control Hosp Epidemiol 2014;35:574-6.
22. Walker S, McGeer A, Simor AE, Armstrong-Evans M, Loeb M. Why are antibiotics prescribed for asymptomatic bacteriuria in institutionalized elderly people? A qualitative study of physicians' and nurses' perceptions. CMAJ 2000;163:273-7.
23. Eyer MM, Läng M, Aujesky D, Marschall J. Overtreatment of asymptomatic bacteriuria: a qualitative study. J Hosp Infect 2016;93:297-303.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:273-277
DOI: 10.4274/BMJ.galenos.2022.2022.2-13

Research

The Impact of Leukocytospermia and Semen Hyperviscosity on Sperm Parameters Among Men with Suspected Infertility

İnfertilite Şüphesi Olan Erkeklerde Lökositopermi ve Semen Hiperviskozitesinin Sperm Parametreleri Üzerine Etkisi

Muhamet Afşin[1], Ayşe Feyda Nursal[2]

[1]University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital, Clinic of Andrology, Diyarbakır, Turkey
[2]Hitit University Faculty of Medicine, Department of Medical Genetics, Çorum, Turkey

ABSTRACT

Objective: Leukocytospermia and semen hyperviscosity (SHV), impair sperm motility and can lead to male infertility. Therefore, this study aimed to evaluate the effect of leukocytospermia, and SHV on semen parameters in men with suspected infertility in Turkey.

Methods: A total of 1,316 semen analysis were included in the study. Sperm parameters were compared in the men with suspected infertility with and without leukocytospermia and SHV.

Results: Leukocytospermia was found in 335 (25.45%) men, and SHV was found in 195 (14.81%) men. Regarding leukocytospermia, there was a significant difference in the liquefaction period and progressive motility among groups. The men with leukocytospermia had increased liquefaction period and sperm concentration compared with men without leukocytospermia (p=0.008, p=0.000, respectively). The ejaculate volume and progressive motility decreased in men with leukocytospermia compared to men without leukocytospermia (p=0.01). Liquefaction period and immotility increased in men with SHV compared to those without SHV (p=0.000, p=0.000, respectively). Progressive motility, non-progressive motility, and total progressive motile sperm count decreased in men with SHV compared to without SHV (p=0.000, p=0.000, p=0.000, respectively).

Conclusion: This study showed that leukocytospermia and SHV frequently occur in men with suspected infertility. Although the total sperm count did not appear to be influenced by leukocytospermia and SHV in our study, and it deserves a detailed investigation in couples with unexplained infertility due to other effective semen parameters.

Keywords: Suspected infertility, leukocytospermia, semen hyperviscosity, semen parameters

ÖZ

Amaç: Lökositospermi ve semen hiperviskozitesi (SHV), sperm motilitesini bozar ve erkek infertilitesine yol açabilir. Bu nedenle, bu çalışmanın amacı Türkiye'de infertilite şüphesi olan erkeklerde lökositospermi ve SHV'nin semen parametreleri üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Çalışmaya toplam 1.316 semen analizi dahil edildi. Lökositospermi ve SHV olan ve olmayan infertilite şüphesi olan erkeklerde sperm parametreleri karşılaştırıldı.

Bulgular: Üç yüz otuz beş (%25,45) erkekte lökositospermi, 195 (%14,81) erkekte SHV saptandı. Lökositospermi açısından gruplar arasında sıvılaşma periyodu ve progresif motilite açısından anlamlı fark vardı. Lökositospermisi olan erkeklerde, lökositospermisi olmayan erkeklere göre daha yüksek sıvılaşma süresi ve sperm konsantrasyonu vardı (sırasıyla p=0,008, p=0,000). Lökositospermisi olan erkeklerde ejakülat hacmi ve progresif motilitesi, lökositospermisi olmayan erkeklere göre azaldı (p=0,01). SHV'li erkeklerde SHV olmayanlara göre sıvılaşma süresi ve hareketsizlik arttı (p=0,000, p=0,000, sırasıyla). SHV'li erkeklerde, SHV olmayanlara kıyasla progresif motilite, ilerleyici olmayan motilite ve total progresif motil sperm sayısı azaldı (p=0,000, p=0,000, p=0,000, sırasıyla).

Address for Correspondence: Ayşe Feyda Nursal, Hitit University Faculty of Medicine, Department of Medical Genetics, Çorum, Turkey
Phone: +90 546 606 75 90 E-mail: feyda.nursal@gmail.com ORCID ID: orcid.org/0000-0001-7639-1122

Cite as: Afşin M, Nursal AF. The Impact of Leukocytospermia and Semen Hyperviscosity on Sperm Parameters Among Men with Suspected Infertility. Med J Bakirkoy 2022;18:273-277

Received: 22.02.2022
Accepted: 23.06.2022

Sonuç: Bu çalışma, infertilite şüphesi olan erkeklerde lökositospermi ve SHV'nin sıklıkla görüldüğünü göstermiştir. Çalışmamızda toplam sperm sayısı lökositospermi ve SHV'den etkilenmemiş gibi görünse de, diğer etkili semen parametreleri nedeniyle açıklanamayan infertilitesi olan çiftlerde ayrıntılı bir araştırmayı hak etmektedir.

Anahtar Kelimeler: Şüpheli infertilite, lökositospermi, semen hiperviskozitesi, semen parametreleri

INTRODUCTION

Infertility is one of the important health problems that couples face worldwide. Infertility is defined as the inability of most couples to become pregnant after at least one year of frequent and unprotected sex and affects about 15% of couples. The main cause of infertility is among 20-50% in cases (1). Several factors impact sperm function, parameters, and then male fertility (2). Molecular mutations, genetic abnormalities, hormonal defects, impaired spermatogenesis, nutritional and some trace element deficiency, structural damages, environmental agents, life styles and obstructive problems are common factors affecting fertilization processes human sperm function (3).

Leukocytospermia is defined by the World Health Organization (WHO) as the presence of 1×10^6 leukocytes/mL in human ejaculate (4). Generally, leukocytospermia may indicate the male urogenital tract and sex glands' inflammation or infection (1). Based on prior studies, it was suggested that leukocytospermia negatively impacts sperm integrity and function (5). In a study found a significant correlation between leukocytospermia and defects in the tail function of sperm (6).

Semen hyperviscosity (SHV), with a coagulated and thick appearance, impacts the human seminal fluid's chemical and physical characteristics (7). Studies have shown the occurrence of SHV in 12%-29% ejaculates (8,9). Semen, which has normal viscose, contributes to sperm fertilization function and process, facilitating the spermatozoa entry into the cervical mucus (10). It maintains sperm swimming speed after mucus penetration (11), prevents the lipid peroxidation reaction (12), controls the surface charge distribution on the sperm membrane in the maturation process and keeps the spermatozoa's chromatin integrity (13).

Therefore, this study aimed to evaluate the effect of leukocytospermia, and SHV, on semen parameters in men with suspected infertility in Turkey.

METHODS

Study Population

This retrospective study was carried out from July 2019 to December 2021 at the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital, Andrology Laboratory. One thousand and three hundred and sixteen males with suspected infertility aged between 18 and 65 years were included in the study. We evaluated men with suspected infertility by dividing them into two groups, as with and without leukocytospermia and SHV after sperm analysis. The principles outlined in the Declaration of Helsinki were followed. The University of Health Sciences Turkey, Clinical Research Ethics Committee of Gazi Yaşargil Training and Research Hospital approved the study (decision no: 11, date: 28.01.2022).

Semen Analysis

Sperm samples were collected from the participants who were sexually abstinent for two-seven days by masturbating into sterilized disposable plastic cups without using any lubricant. Semen samples taken from the participants were examined in conformity with WHO criteria after liquefaction. The semen samples were first homogenized by pipetting with a Pasteur pipette. Approximately 10 µL of semen was pipetted and placed on the Makler camera (counting chamber) and sealed with a glass lid to determine the count and motility. Spermatozoa in 10 squares were counted through the x20 lens of the light microscope (Olympus CX31), and the results were expressed in millions. It was evaluated that sperm parameters including viscosity, leucocyte count, sperm concentration, total sperm count, motility, immotilty, and total progressive motile sperm count (TPMSC).

Leukocytospermia Analysis

A practical and reliable method for distinguishing leucocytes in the semen Papanicolaou dyeing method, which is a method, was used. A light microscope was used to distinguish spermatids and spermatocytes from polymorphonuclear leukocytes in a Papanicolaou-stained semen smear. The procedure is based mainly on the staining color, nuclear size, and shape differences. Polymorphonuclear leukocytes are stained a bluish color in contrast to the more pinkish color of spermatids.

Viscosity Analysis

After liquefaction, semen was aspirated into a disposable plastic pipette. The viscosity level is determined by the filament formed when it is left to drip (4). While a normal semen sample leaves small and separate drops from the pipette when the SHV drop forms a thread longer than 2 cm.

Statistical Analysis

The data obtained in the study were expressed as the arithmetic mean ± standard deviation. The Statistical Package Program for the Social Sciences (version 21) was used for statistical analysis. The conformity of the data to the normal distribution was analyzed using the Shapiro-Wilk test, and the homogeneity was analyzed by Levene's test. Student' t-test was used for statistical analysis. The significance was taken as $p \leq 0.05$.

RESULTS

A total of 1,316 semen analyses were included in the study. Leukocytospermia was found in 335 (25.45%) men, and SHV was found in 195 (14.81%) men. Sperm parameters were compared in the men with suspected infertility with and without leukocytospermia and SHV. Regarding leukocytospermia, there was a significant difference in the liquefaction period and progressive motility among groups. The men with leukocytospermia had increased liquefaction period and sperm concentration compared with men without leukocytospermia (p=0.008, p=0.000, respectively). The ejaculate volume and progressive motility decreased in men with leukocytospermia compared to men without leukocytospermia (p=0.01). The sperm parameters of men with and without leukocytospermia are presented in Table 1.

Then, we evaluated the sperm parameters in men with infertility who were suspected of SHV. For SHV, the liquefaction period, progressive motility, nonprogressive motility, immotility, and TPMSC were statistically different between the groups. Liquefaction period and immotility increased in men with SHV compared to those without SHV (p=0.000, p=0.000, respectively). Progressive motility, non-progressive motility, and TPMSC decreased in men with SHV compared to without SHV (p=0.000, p=0.000, p=0.000, respectively). The results are shown in Table 2.

DISCUSSION

The genitourinary tract's infectious process may contribute to males' fertility and reproductive function. Generally, leukocytospermia is assumed to indicate underlying genitourinary infection, and its incidence vary between 22 and 30%. This is commonly related to the seminal vesicle, epididymis, or prostate infection (14). Due to the common leukocytospermia in infertile men, whether the seminal leukocyte presence is correlated with the quality of semen may be questioned. Some studies' results show a the negative impact of leukocytes on the quality of semen due to the reactive oxygen species (ROS) presence. Activated leukocytes secrete protease, cytokines, and ROS, leading to damage sperm through deoxyribonucleic acid (DNA) fragments and lipid peroxidation (15). According to Agarwal et al. (16), patients presenting with low-level leukocytospermia have seminal oxidative stress. Although the present WHO guidelines do not categorize these patients as leukocytospermic, these men benefit from antibiotic treatment, testing for antioxidant supplements, or bacterial cultures to decrease the sperm DNA fragmentation induced by ROS and improve their fertility chances.

Leukocytospermia have been reported to hinder the spermatozoa's fertilization potential by interfering with sperm and egg fusion and the acrosome reaction (7,17). For this reason, the leucocytes presence in seminal plasma is

Table 1. Semen analysis of groups according to leukocytospermia

Semen quality parameters	Without leukocytospermia (n=981)	With leukocytospermia (n=335)	p
Abstinence period (day), mean ± SD	3.27±0.49	2.23±0.5	0.27
Age (year), mean ± SD	30.75±6.68	29.87±7.48	0.05
Liquefaction period (minute), mean ± SD	34.79±10.54	36.59±10.75	0.008
Ejaculate volume (mL), mean ± SD	3.02±1.77	2.77±1.38	0.01
Sperm concentration (million/mL), mean ± SD	35.8±30.46	43.28±32.69	0.00
Total sperm count (million), mean ± SD	101.33±95.57	109.23±87.54	0.18
Motility (%)			
Progressive (%), mean ± SD	47.72±20.8	44.97±17.90	0.02
Non-progressive (%), mean ± SD	10.28±6.64	9.96±5.97	0.41
Immotility (n, %), mean ± SD	41.77±20.13	45.24±18.23	0.05
TPMSC (million), mean ± SD	54.45±62.93	51.53±47.04	0.37

SD: Standard deviation, TPMSC: Total progressive motile sperm count

Table 2. Semen analysis of groups according to SHV

Semen quality parameters	Without SHV (n=1,121)	With SHV (n=195)	p
Abstinence period (day), mean ± SD	3.26±0.49	3.27±0.49	0.8
Age (year), mean ± SD	30.52±6.85	30.55±7.19	0.95
Likefaction period (minute), mean ± SD	32.27±6.98	52.30±11.82	0.00
Ejaculate volume (mL), mean ± SD	2.94±1.73	3.06±1.41	0.33
Sperm concentration (million/mL), mean ± SD	38.21±31.51	34.75±29.32	0.15
Total sperm count (million), mean ± SD	103.78±94.13	100.00±90.19	0.60
Motility (%)			
Progressive (%), mean ± SD	49.00±19.56	35.66±19.97	0.00
Non-progressive (%), mean ± SD	10.37±6.41	9.24±6.80	0.03
Immotility (%), mean ± SD	40.52±18.8	54.9±20.46	0.00
TPMSC (million), mean ± SD	56.34±61.24	38.31±43.5	0.00

SD: Standard deviation, SHV: Semen hyperviscosity, TPMSC: Total progressive motile sperm count

an important prognostic factor for failed embryo transfer and *in vitro* fertilization (18). A study by Ziyyat et al. (19) paradoxically decreased sperm motility in semen samples with a higher threshold of 1×10^6 leukocytes/mL and found that sperm motility increased among the semen samples with moderate leukocytospermia. Lackner et al. (20) found that the concentration-dependent association of leukocyte concentration was positively associated with sperm motility and morphology.

The chemical and physical characteristics of seminal fluid can be seriously impaired by SHV. Recent studies show that 12%-29% of ejaculates had SHV as the main cause of male infertility (21). In this regard, more research attention has been paid to it because of its serious effect on sperm function. The probable causes of SHV are infection, inflammation, and dysfunction of the immune system or the male accessory glands (8). More importantly, it seems that SHV is related to decreased sperm motility, probably because the trapping effect prevents the progression of normal sperm through the female genital tract (21). Gonzales (22) and Andrade-Rocha (8) found that fructose levels in SHV were reduced and hypothesized that the seminal vesicles inadequately functioned as the explanation. A study by Lampiao and Chisaka (23) found significantly higher progressive motility, normal morphology, sperm concentration, viability, and total motility in the normal viscosity group than in the abnormal viscosity group. A study found significantly reduced sperm and vitality sperm motility while SHV significantly increased polymorphonuclear granulocyte elastase levels (24).

In this study, we evaluated the men with suspected infertility in leukocytospermia and SHV. Our rates of leukocytospermia and SHV were consistent with the literature. There was a significant difference among the groups under study regarding leukocytospermia and SHV. This study demonstrated that leukocytospermia had a negative effect on the liquefaction period, sperm concentration, ejaculate volume, and progressive motility. Men with leukocytospermia had increased liquefaction period and sperm concentration compared with men without leukocytospermia, whereas the ejaculate volume and progressive motility decreased in men with leukocytospermia compared with those without leukocytospermia (Table 1). Also, this study clearly showed a significant negative correlation between SHV and liquefaction period, immotility, progressive motility, non-progressive motility, and TPMSC. The liquefaction period and immotility increased in men with SHV compared to those without SHV, whereas progressive motility, non-progressive motility, and TPMSC decreased in men with SHV compared to those without SHV (Table 2).

One limitation of this study was that it was retrospective. However, the high number of samples will help us understand the factors affecting suspected infertility.

CONCLUSION

This study showed that leukocytospermia and SHV frequently occur in men with suspected infertility. Although total sperm count did not appear to be influenced by leukocytospermia and SHV in our study, deserves a detailed investigation in couples with unexplained infertility due to other effective semen parameters.

ETHICS

Ethics Committee Approval: The University of Health Sciences Turkey, Clinical Research Ethics Committee of Gazi Yaşargil Training and Research Hospital approved the study (decision no: 11, date: 28.01.2022).

Informed Consent: Retrospective study.

Authorship Contributions

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

Conflict of Interest: The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

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

REFERENCES

1. Jung JH, Kim MH, Kim J, Baik SK, Koh SB, Park HJ, et al. Treatment of Leukocytospermia in Male Infertility: A Systematic Review. World J Mens Health 2016;34:165-72.
2. Tahmasbpour E, Balasubramanian D, Agarwal A. A multi-faceted approach to understanding male infertility: gene mutations, molecular defects and assisted reproductive techniques (ART). J Assist Reprod Genet 2014;31:1115-37.
3. Agarwal A, Roychoudhury S, Sharma R, Gupta S, Majzoub A, Sabanegh E. Diagnostic application of oxidation-reduction potential assay for measurement of oxidative stress: clinical utility in male factor infertility. Reprod Biomed Online 2017;34:48-57.
4. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: World Health Organization; 2010.
5. Brunner RJ, Demeter JH, Sindhwani P. Review of Guidelines for the Evaluation and Treatment of Leukocytospermia in Male Infertility. World J Mens Health 2019;37:128-37.
6. Aziz N, Agarwal A, Lewis-Jones I, Sharma RK, Thomas AJ Jr. Novel associations between specific sperm morphological defects and leukocytospermia. Fertil Steril 2004;82:621-7.
7. Layali I, Tahmasbpour E, Joulaei M, Jorsaraei SG, Farzanegi P. Total antioxidant capacity and lipid peroxidation in semen of patient with hyperviscosity. Cell J 2015;16:554-9.
8. Andrade-Rocha FT. Physical analysis of ejaculate to evaluate the secretory activity of the seminal vesicles and prostate. Clin Chem Lab Med 2005;43:1203-10.
9. Esfandiari N, Burjaq H, Gotlieb L, Casper RF. Seminal hyperviscosity is associated with poor outcome of in vitro fertilization and embryo transfer: a prospective study. Fertil Steril 2008;90:1739-43.
10. Overstreet JW, Coats C, Katz DF, Hanson FW. The importance of seminal plasma for sperm penetration of human cervical mucus. Fertil Steril 1980;34:569-72.
11. Du Plessis SS, Gokul S, Agarwal A. Semen hyperviscosity: causes, consequences, and cures. Front Biosci (Elite Ed) 2013;5:224-31.
12. Jones R, Mann T, Sherins R. Peroxidative breakdown of phospholipids in human spermatozoa, spermicidal properties of fatty acid peroxides, and protective action of seminal plasma. Fertil Steril 1979;31:531-7.
13. Huret JL. Nuclear chromatin decondensation of human sperm: a review. Arch Androl 1986;16:97-109.
14. Gambera L, Serafini F, Morgante G, Focarelli R, De Leo V, Piomboni P. Sperm quality and pregnancy rate after COX-2 inhibitor therapy of infertile males with abacterial leukocytospermia. Hum Reprod 2007;22:1047-51.
15. Agarwal A, Virk G, Ong C, du Plessis SS. Effect of oxidative stress on male reproduction. World J Mens Health 2014;32:1-17.
16. Agarwal A, Mulgund A, Alshahrani S, Assidi M, Abuzenadah AM, Sharma R, et al. Reactive oxygen species and sperm DNA damage in infertile men presenting with low level leukocytospermia. Reprod Biol Endocrinol 2014;12:126.
17. Sharma RK, Pasqualotto AE, Nelson DR, Thomas AJ Jr, Agarwal A. Relationship between seminal white blood cell counts and oxidative stress in men treated at an infertility clinic. J Androl 2001;22:575-83.
18. Rodriguez-Martinez H, Martinez EA, Calvete JJ, Peña Vega FJ, Roca J. Seminal Plasma: Relevant for Fertility? Int J Mol Sci 2021;22:4368.
19. Ziyyat A, Barraud-Lange V, Sifer C, Ducot B, Wolf JP, Soufir JC. Paradoxical increase of sperm motility and seminal carnitine associated with moderate leukocytospermia in infertile patients. Fertil Steril 2008;90:2257-63.
20. Lackner JE, Herwig R, Schmidbauer J, Schatzl G, Kratzik C, Marberger M. Correlation of leukocytospermia with clinical infection and the positive effect of antiinflammatory treatment on semen quality. Fertil Steril 2006;86:601-5.
21. Beigi Harchegani A, Rahmani H, Tahmasbpour E, Shahriary A. Hyperviscous Semen Causes Poor Sperm Quality and Male Infertility through Induction of Oxidative Stress. Curr Urol 2019;13:1-6.
22. Gonzales GF. Function of seminal vesicles and their role on male fertility. Asian J Androl 2001;3:251-8.
23. Lampiao F, Chisaka J. Incidence and impact of hyperviscosity on sperm parameters of Malawian men seeking assisted reproduction. Afr Health Sci 2020;20:1-3.
24. Mahran Z, Eraki Saleh ME. Human semen hyperviscosity: prevalence and effects on physical and biochemical semen parameters in subfertile Egyptian men. Egypt J Dermatol Venerol 2014;34:135-9.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:278-284
DOI: 10.4274/BMJ.galenos.2022.2022.2-20

Research

Does the "Risk-based Management Model" for Residual Disease in Patients with High-grade Cervical Intraepithelial Lesions Cause Overtreatment?

Yüksek Dereceli Servikal İntraepitelyal Lezyonları Olan Hastalarda Rezidüel Hastalık için "Risk Bazlı Yönetim Modeli" Aşırı Tedaviye Neden Olur mu?

Mehmet Adıyeke[1], Suna Yıldırım Karaca[1,2], Sümeyye Ekmekci[3], Muzaffer Sancı[1]

[1]University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Obstetrics and Gynaecology, İzmir, Turkey
[2]Ege University Institute of Health Sciences, Department of Stemcell, İzmir, Turkey
[3]University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Pathology, İzmir, Turkey

ABSTRACT

Objective: This study aimed to determine the residual disease status of high-grade cervical intraepithelial lesion-positive (HSIL) patients with margin positive at first cervical excision.

Methods: This study included patients with HSIL-positive surgical margins following cervical excision procedures between March 2015 and August 2020. The patients with normal histopathology results, cervical intraepithelial neoplasia (CIN)1, CIN2-3 with negative surgical margins, and confirmed cervical malignancy were excluded. HSIL in the second cervical excision pathology was accepted as a residual disease. Demographic and clinical characteristics, pathology results and human papilloma virus genotypes of the patients were assessed.

Results: Surgical margin was positive in 354 (21.3%) of 1,656 patients who underwent cervical excision procedures with the indication of HSIL. Computer-based medical records of 330 patients who underwent the second cervical excision procedure from these patients were reviewed and analyzed. Residual disease was diagnosed in 31.3% (31/99) patients whose first cervical biopsy was CIN2 and in 48.4% (112/231) patients with CIN3. Additionally, 3 of the patients with CIN3 had microinvasive cervical cancer in final pathology. In patients with residual disease (≥ CIN2), the rate of CIN3 at first excision, the rate of smokers, and the rate of glandular involvement in the excision specimen was higher (respectively; p=0.04, p=0.01, p=0.03).

Conclusion: Residual disease high in patients with the first cervical excision histopathology of CIN3, endocervical glandular involvement, and previously or currently smoked. In the disease management of women with CIN3 and positive margins, re-excision rather than follow-up may be a better option.

Keywords: Cervical intraepithelial neoplasia, residuel disease, human papilloma virus

ÖZ

Amaç: Bu çalışmanın amacı, ilk servikal eksizyonda cerrahi sınır pozitif olan yüksek dereceli servikal intraepitelyal lezyon pozitif (HSIL) hastaların rezidüel hastalık durumunu belirlemektir.

Gereç ve Yöntem: Bu çalışmaya Mart 2015 ile Ağustos 2020 tarihleri arasında servikal eksizyon işlemleri sonrası HSIL cerrahi sınırı pozitif olan hastalar dahil edildi. Histopatoloji sonuçları normal, servikal intraepitelyal neoplazi (CIN)1, cerrahi sınırı negatif olan CIN2-3 ve doğrulanmış servikal malignitesi olan hastalar çalışma dışı bırakıldı. İkinci servikal eksizyon patolojisinde HSIL rezidüel hastalık olarak kabul edildi. Hastaların demografik ve klinik özellikleri, patoloji sonuçları ve insan papillom virüsü genotipleri incelendi.

Bulgular: HSIL endikasyonu ile servikal eksizyon işlemi uygulanan 1.656 hastanın 354'ünde (%21,3) cerrahi sınır pozitifti. Bu hastalardan ikinci servikal eksizyon prosedürü uygulanan 330 hastanın bilgisayar tabanlı tıbbi kayıtları incelendi ve analiz edildi. İlk servikal biyopsisi CIN2 olan hastaların %31,3'ünde (31/99), CIN3'ü olan hastaların %48,4'ünde (112/231) rezidüel hastalık tanısı konuldu. Ayrıca CIN3'lü hastaların 3'ünde son patolojide mikroinvaziv serviks kanser vardı. Rezidüel hastalığı olan hastalarda (≥ CIN2), ilk eksizyonda CIN3 oranı, sigara içenlerin oranı ve eksizyon örneğinde glandüler tutulum oranı daha yüksekti (sırasıyla; p=0,04, p=0,01, p=0,03).

Address for Correspondence: Mehmet Adıyeke, University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Obstetrics and Gynaecology, İzmir, Turkey
Phone: +90 505 616 21 10 E-mail: mehmetadiyeke@gmail.com ORCID ID: orcid.org/0000-0003-2200-7097

Cite as: Adıyeke M, Yıldırım Karaca S, Ekmekci S, Sancı M. Does the "Risk-based Management Model" for Residual Disease in Patients with High-grade Cervical Intraepithelial Lesions Cause Overtreatment?. Med J Bakirkoy 2022;18:278-284

Received: 24.02.2022
Accepted: 23.06.2022

Sonuç: İlk servikal eksizyon histopatolojisi CIN3 olan, endoservikal glandüler tutulumu olan ve daha önce veya halen sigara içen hastalarda rezidüel hastalık oranı yüksektir. CIN3 ve pozitif sınırlara sahip kadınların hastalık yönetiminde takip yerine yeniden eksizyon daha iyi bir seçenek olabilir.

Anahtar Kelimeler: Servikal intraepitelyal lezyon, rezidüel hastalık, insan papillom virüsü

INTRODUCTION

The adoption of risk-based cervical cancer screening programs has significantly reduced the incidence of cervical cancer (1). However, cervical cancer; it is still an important health problem in women without appropriate follow-up and treatment, and women with recurrent or residual disease (2,3). The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends treatment for patients with histologically diagnosed high-grade cervical intraepithelial lesions (HSIL, includes CIN2-3) (1). The most commonly used treatment method is loop electrosurgical excision procedure (LEEP) of the transformation zone or cold knife conization (CKC) (4,5). However, these procedures may not remove the lesions and may result in positive surgical margins (5).

In a large population-based study, it was shown that 23% of women had positive surgical margins after cervical excision (6). Even in patients whose lesion is removed, the risk of recurrence of high-grade lesions is higher than in the general population (6). Therefore, the positivity of surgical margins, which is predisposing to residual disease, is a legitimate cause for anxiety for the patient. However, as it is difficult to find a balance between iatrogenic harm and therapeutic efficacy, there has not yet been reached consensus on the further management of these patients (1). Therefore, the management strategy ranges from follow-up cytology to second conization and even hysterectomy (1). While performing cytological follow-up may miss a more severe underlying disease, repeated excisions may cause surgical complications and increased morbidity.

The main question for patients with positive surgical margins is their residual disease status in patients after excision. In this study, we immediately performed a second surgical procedure on patients with positive surgical margins after the first cervical excision. Thus, it determines the baseline residual disease risk in patients with positive surgical margins.

METHODS

Study Design and Patient Selection

Pathology records of the patients who underwent LEEP or CKC between March 2015-August 2020 were retrospectively screened. CIN2 and 3 cases with performed the second excision procedures due to positive margins were included in the study. Patients with normal histopathology results, CIN1, CIN2-3 with negative surgical margins, and confirmed cervical malignancy were excluded. The study protocol was approved by our institutional review board (University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Non-Interventional Research Ethics Committee-decision no: 2021/08-10, date: 16.08.2021). Informed consent could not be obtained from the patients because of the retrospective design of the study.

The surgical margin was positive in 354 (21.3%) of 1,656 patients who underwent cervical excision procedure for HSIL during the study period. Of these patients, the data of 330 patients who underwent a second surgical procedure in our institution and met the inclusion criteria were analyzed.

Interventions

Initial LEEP and CKC

Preoperative evaluation, including cervical cytology, colposcopy and colposcopy-directed cervical biopsy was underwent in all patients. Schiller test was performed to determine the borders of the excision area before conization. LEEP was performed under local anesthesia and CKC was performed under general anesthesia by residents in the operating room under expert supervision. These procedures were conducted in a standard manner as previously described (7). Conization specimens were marked with a suture at 12 o'lock to locate the lesions. After all, conization, endocervical curettage was performed using a uterine curette (size 0) and the samples were sent separately for histopathological examination. Hemostasis was obtained by electrocoagulation.

Human Papilloma Virus (HPV) Test

To identify HPV genotypes, we analyzed cervical samples preoperatively using Hybrid Capture 2 for HPV types 16, 18, and 12 other high-risk HPV (hrHPV) (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). HPV genotyping was divided into two categories: HPV type 16/18 and non-HPV-16/18 oncogenic types.

Further Surgical Procedures

The type of the second surgical procedure to be performed for patients with positive margins was based on the clinical and pathological characteristics of each patient. All patients

underwent a second surgery within 30 days of the first excision. Second surgical procedures included CKC, LEEP, or hysterectomy, depending on the suitability of the cervix.

Pathological Examination

Positive surgical margins were defined as the presence of CIN2 or CIN3 at the ectocervix. The specimens were examined for cone depth, histological grade (CIN2 or CIN3), surgical margin state and the presence or absence of CIN2 and CIN3 in endocervical curettage (ECC) sampling were recorded. According to the pathology reports of the second operation, the patients were divided into two groups as ≤ CIN1 and ≥ CIN2. CIN1 lesions included CIN1 and normal biopsy results, whereas CIN2 lesions included CIN2, CIN3, and microinvasive cervical cancer.

Statistical Analysis

All statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows (SPSS, Inc., Chicago, IL). The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov/Shapiro-Wilk's test. Differences in the means of the continuous variables were assessed using the Mann-Whitney U test or independent samples t-test; the difference in the categorical variables was assessed using the chi-square test. $P<0.05$ was considered statistically significant.

RESULTS

Surgical margins were positive in 354 (21.3%) of 1656 patients who underwent cervical excision for HSIL during the study period. Computer-based medical records of 330 patients who underwent the second cervical excision procedure were reviewed and analyzed. Re-excision procedure was not performed in 24 patients with positive margins. The first lesions of all these patients were CIN2, and CIN persisted in 7 patients in their follow-up 1 year later. The median age of the patients was 44 (25^{th}-75^{th} percentile, 36-49) and 67.9% were premenopausal patients. Other demographic characteristics are shown in Table 1. LEEP (88.7%, 293 patients) or CNK (11.3%, 37 patients) was used as the initial cervical excision procedure. HPV genotyping was performed on all patients before the procedure and the most detected genotype was HPV 16 (74.5%, 246 patients). The mean depth of the first cervical excision pathology specimen of margin-positive patients was 11.1±4.7 mm. In the histopathological results after the first cervical excision, 30% of the patients (99 patients) reported CIN2 and 70% of had CIN3. Additionally, 73.3% of patients had a glandular involvement at the first cervical excision (Table 2).

In the analysis of the final pathology results after the second cervical excision, residual disease was detected in 31.3% (31/99) of the patients whose first cervical histopathology was CIN2. However, 48.4% (112/231) of the patients whose first cervical excision histopathological result was CIN3 had residual disease. Additionally, microinvasive cervix ca be detected in the final pathology in 3 of the patients with CIN 3 (Table 3).

Table 1. Baseline demographic characteristics of margin positive patients

Characteristic	Values
Number of patients	330
Age (years)	
Median (min-max)	44 (24-78)
25^{th}-75^{th} percentiles	36-49
Gravida	
Median (min-max)	3 (0-12)
25^{th}-75^{th} percentiles	2-3
Parity	
Median (min-max)	2 (0-8)
25^{th}-75^{th} percentiles	2-3
Smoking status of patients	
Never smoked	171 (51.8%)
Currently or previously smoked	90 (27.2%)
Not known	69 (21%)
Menopausal status of patients	
Premenopausal	224 (67.9%)
Postmenopausal	106 (32.1%)

Min-max: Minimum-maximum, the data is presented as median (25^{th} percentile; 75^{th} percentile) or ratio

Margin-positive patients were divided into two groups according to the final pathology result after the second excision, as those with residual disease (≥ CIN2) and those without (≤ CIN1). Both groups were compared according to their demographic and pathological results. In the group with residual disease, the rate of CIN3 at the first excision, the rate of smokers, and the rate of glandular involvement in the excision specimen was higher. (respectively; $p=0.04$, $p=0.01$, $p=0.03$). There was no statistical difference between the groups in terms of age, parity, gravida, menopausal status, endocervical canal pathology and depth of the first cervical excision specimen (Table 4).

DISCUSSION

The positivity of the surgical margin in the histopathology of patients who underwent cervical excision procedure with the indication of HSIL is the most important determinant of

Table 2. Pathology results and HPV genotypes of margin positive patients

Characteristic	Values
Surgical technique (initial procedure)	
LEEP	293 (88.7%)
CKC	37 (11.3%)
HPV 16 +	246 (74.5%)
HPV 18 +	225 (68.1%)
Non HPV 16/18 +	84 (25.4%)
Depth of initial leep specimen (mean ± SD, mm)	11.1±4.7
Presence of glandular involvement in the initial procedure	242 (73.3%)
Initial cervical excision (LEEP/CKC) pathology	
CIN2	99 (30%)
CIN3	231 (70%)
ECC	
≤ CIN1	195 (59%)
≥ CIN2	135 (41%)
Second cervical pathology	
≤ CIN1	187 (56.6%)
≥ CIN2	143 (43.4%)

HPV: Human papilloma virus, SD: Standard deviation, LEEP: Loop electrosurgical excision procedure, CKC: Cold knife conization, CIN: Cervical intraepithelial neoplasia

CIN recurrence. Guidelines could not reach a consensus on whether these patients should undergo a second surgical procedure. In this study, we immediately performed a second surgical procedure on margin-positive patients and provided an understanding of the residual disease status. Our study showed residual disease in 31.3% of patients with initial histopathology of CIN2 and 48.4% of patients with CIN3. Microinvasive cervix ca be present in 3 patients with CIN 3. Additionally, the rate of glandular involvement in the first excision sample was higher in the group with residual disease.

Based on the risk-based management model, ASCCP; states that it may be preferable to follow margin-positive patients with cytology and ECC at 4-6 month intervals, at the same time re-excision is acceptable and hysterectomy can be performed if re-excision is impossible (1). However, the International Federation of Gynecology and Obstetrics recommends reoperation in CIN3 patients with positive surgical margins (8). In fact, the main reason for all these discussions is that the "wait and see strategy" carries a high risk of HSIL margin-positive patients. Periodic follow-up may increase the recurrence rate and patient anxiety and may miss a more severe underlying disease. However, repetitive surgery can cause complications and morbidity. Additionally, the goal of reaching the negative surgical margin may require larger excisions, but this may also increase the risk of obstetric harm.

Previous studies have shown that margin-positive HSIL patients have a residual disease rate of 44-67% on histopathology after the second cervical excision (9,10). In our study, the residual disease rate was 43.3% (143/330). In patients with initial cervical excision pathology CIN3, the residual disease rate was 48.4%. Moreover, 3 of these patients were diagnosed with microinvasive cervix ca at the second excision. In our study, we did not detect residual disease in 68.7% of patients with positive margins for CIN2 and in 51.6% of patients with positive margins for CIN3. Some authors suggest that vaginal acidity and thermal destruction will promote epithelial regeneration of the cervix (11). Especially in CIN2 margin positive patients, the regression rates of the lesions seen after the second excision were remarkable. However, ≥ CIN3 was detected in 34.1% (79/231) of the patients whose initial pathology was CIN3. Considering that the risk of progression to invasive carcinoma depends on the severity and size of the CIN lesion, and that approximately one-third of women with untreated CIN3 will eventually develop invasive cervical cancer, our findings suggest that secondary surgical intervention should be performed in patients with margin-positive CIN3 lesions.

Table 3. Classification of second cervical excision pathologies of HSIL margin positive patients

Initial cervical excision pathology	Second cervical pathology					
	Normal	CIN1	CIN2	CIN3	Microinvasive ca	Total
CIN2	44 (44.4%)	24 (24.3%)	26 (26.3%)	5 (5%)	0	99 (100%)
CIN3	53 (23%)	66 (28.5%)	33 (14.2%)	76 (33%)	3 (1.3%)	231 (100%)
Total	97	90	59	81	3	330

CIN: Cervical intraepithelial neoplasia, HSIL: High-grade cervical intraepithelial lesion

Table 4. Comparison of clinical and pathological results of magin positive patients with and without residual disease

Characteristic	Patients with residual disease (n=143)	Patients without residual disease (n=187)	p-value
Age (years)	43 (25-78)	44 (24-76)	0.12
Gravida	3 (1-12)	3 (0-11)	0.21
Parity	2 (0-7)	2 (0-8)	0.33
Currently or previously smoked	49 (34.2%)	41 (21.9%)	0.01
Menopausal status of patients			
Premenopausal	92 (64.3%)	132 (70.5%)	0.22
Postmenopausal	51 (35.7%)	55 (29.4%)	
Surgical technique (initial procedure)			
LEEP	136 (95.1%)	157 (83.9%)	0.02
CKC	7 (4.9%)	30 (16.1%)	
Initial cervical pathology			
CIN2	31 (21.6%)	68 (36.3%)	0.04
CIN3	112 (78.4%)	119 (63.7%)	
ECC			
≤ CIN1	92 (64.3%)	103 (55%)	0.09
≥ CIN2	51 (35.7%)	84 (45%)	
Presence of glandular involvement in the initial pathology	117 (81.8%)	125 (66.8%)	0.03
Depth of initial cervical excision Specimen (mean ± SD, mm)	11±4.6	11.5±4.9	0.5
HPV 16 +	111 (77.6%)	135 (72.1%)	0.3
HPV 18 +	99 (69.2%)	119 (63.6%)	0.3
Non HPV 16/18 +	38 (26.5%)	46 (24.5%)	0.6

HPV: Human papilloma virus, SD: Standard deviation, LEEP: Loop electrosurgical excision procedure, CKC: Cold knife conization, CIN: Cervical intraepithelial neoplasia, ECC: Endocervical Curettage

Another histopathological finding that was significantly higher in residual disease in our study was the presence of cervical glandular involvement. Levine et al. (12) reported that endocervical glandular involvement in cervical excision specimens was associated with a higher incidence of positive margins and poor response to treatment. In our study, the rate of glandular involvement was higher in margin-positive patients with residual disease. Endocervical glands are located in the cervical stroma below the basement membrane of normal squamous epithelium and may be involved by neoplastic lesions. The involvement of such glands with high-grade CIN may mimic invasive disease and be misdiagnosed as invasive cervical carcinoma. Lu et al. (4) and Kim et al. (13) argued that the glandular involvement is not a significant prognostic value, while Demopoulos et al. (14) reported that glandular involvement is a valuable prognostic factor for residual and recurrent disease and is mostly associated with high-grade CIN. The involvement of the endocervical glands can be considered a sign of the diffuse nature of the disease with a higher propensity for involvement of surrounding tissues. Considering this situation, the risk of residual disease seems to be higher in the presence of glandular involvement in patients with positive surgical margins, as in our study.

Age and menopausal status are another factor emphasized in relation to residual disease risk. Zhu et al. (15) reported in their study that increasing age is a high-risk factor for persistent HSIL after LEEP. Similarly, Chen et al. (16) reported that being older than 50 years is a risk factor for residual lesions. As the authors explain the relationship between increasing age and menopausal status with residual disease; they claimed that the decrease in estrogen levels in menopause causes upward migration of the cervical transformation zone and HSIL lesions settle higher and form higher permanent lesions (15,16). However, in our study, we

did not find an association between residual disease and age, and menopausal status.

Recently, a systematic review compared the efficacy and safety of various excisional treatments for residual disease for treating cervical dysplasia (17). They observed that CKC reduced the risk of residual disease compared to LEEP. Women undergoing LEEP had an approximately 2-fold increase in positive margin rate compared with CKC. In contrast, LEEP is faster, inexpensive and requires less expertise than cold conization (18). LEEP is mostly performed as the first cervical excision procedure in our institution. Therefore, although our data is not homogeneous in terms of the first surgical excision procedure; residual disease after CKC is 18% (7/37) compared with 46% (136/293) after LEEP. Although CKC appears advantageous in terms of residual disease, meta-analyses have determined that the depth of excision is associated with the risk of preterm delivery and that CKC carries a particularly high risk (19,20). There several studies have investigated the optimal excision depth to achieve clear surgical margins Papoutsis et al. (21) reported that the depth of conization should be at least 10 mm to provide negative surgical margins. In our study, patients with and without residual disease were 11 and 11.5 mm, respectively, and did not predict residual disease.

Our findings showed that the rate of residual disease is high in patients with the first cervical excision histopathology of CIN 3, endocervical glandular involvement, and previously or currently smoked. Almost all the patients were hrHPV positive. Previous studies have already shown that the presence of HPV is important for patient follow-up rather than pre-procedure. A comprehensive systematic review conducted in 2017 reported the failure of treatment with the indication of HSIL (margin positivity); it was reported that post-treatment hrHPV was predicted more accurately than surgical margin positivity (22).

Strengths of our study include a consistent approach used to treat HSIL and the availability of expert pathological review. Moreover, all patients underwent reoperation within 30 days for more accurate identification of residual disease and little chance of new disease or regression. The limitations were because the study was retrospective, over a long time, and limited to a single institution. However, a prospective study design is difficult given the relative rarity of margin positivity.

CONCLUSION

In conclusion, our findings suggest that it is appropriate to recommend repeat excision rather than a follow-up for women with CIN 3 and positive margins.

ETHICS

Ethics Committee Approval: The study protocol was approved by our institutional review board (University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Non-Interventional Research Ethics Committee-decision no: 2021/08-10, date: 16.08.2021).

Informed Consent: Informed consent could not be obtained from the patients because of the retrospective design of the study.

Authorship Contributions

Concept: M.A., M.S., Design: M.A., M.S., Data Collection or Processing: S.Y.K., S.E., Literature Search: S.Y.K., Writing: M.A., S.Y.K.

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

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

REFERENCES

1. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2013;17(5 Suppl 1):S1-S27.
2. Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. Lancet Oncol 2007;8:985-93.
3. Serati M, Siesto G, Carollo S, Formenti G, Riva C, Cromi A, et al. Risk factors for cervical intraepithelial neoplasia recurrence after conization: a 10-year study. Eur J Obstet Gynecol Reprod Biol 2012;165:86-90.
4. Lu CH, Liu FS, Tseng JJ, Ho ES. Predictive factors for residual disease in subsequent hysterectomy following conization for CIN III. Gynecol Oncol 2000;79:284-8.
5. Ayhan A, Boynukalin FK, Guven S, Dogan NU, Esinler I, Usubutun A. Repeat LEEP conization in patients with cervical intraepithelial neoplasia grade 3 and positive ectocervical margins. Int J Gynaecol Obstet 2009;105:14-7.
6. Kocken M, Helmerhorst TJ, Berkhof J, Louwers JA, Nobbenhuis MA, Bais AG, et al. Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: a long-term multi-cohort study. Lancet Oncol 2011;12:441-50.
7. Kobak WH, Roman LD, Felix JC, Muderspach LI, Schlaerth JB, Morrow CP. The role of endocervical curettage at cervical conization for high-grade dysplasia. Obstet Gynecol 1995;85:197-201.
8. Benedet JL, Bender H, Jones H 3rd, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2000;70:209-62.
9. Tyler LN, Andrews N, Parrish RS, Hazlett LJ, Korourian S. Significance of margin and extent of dysplasia in loop electrosurgery excision procedure biopsies performed for high-grade squamous intraepithelial lesion in predicting persistent disease. Arch Pathol Lab Med 2007;131:622-4.
10. Tasci T, Turan T, Ureyen I, Karalok A, Kalyoncu R, Boran N, et al. Is there any predictor for residual disease after cervical conization

with positive surgical margins for HSIL or microinvasive cervical cancer? J Low Genit Tract Dis 2015;19:115-8.

11. Sherman ME, Wang SS, Tarone R, Rich L, Schiffman M. Histopathologic extent of cervical intraepithelial neoplasia 3 lesions in the atypical squamous cells of undetermined significance low-grade squamous intraepithelial lesion triage study: implications for subject safety and lead-time bias. Cancer Epidemiol Biomarkers Prev 2003;12:372-9.
12. Levine PH, Waisman J, Mittal K. Significance of the cytologic diagnosis of endocervical glandular involvement in high-grade squamous intraepithelial lesions. Diagn Cytopathol 2002;26:217-21.
13. Kim HJ, Kim KR, Mok JE, Nam JH, Kim YT, Kim YM, et al. Pathologic risk factors for predicting residual disease in subsequent hysterectomy following LEEP conization. Gynecol Oncol 2007;105:434-8.
14. Demopoulos RI, Horowitz LF, Vamvakas EC. Endocervical gland involvement by cervical intraepithelial neoplasia grade III. Predictive value for residual and/or recurrent disease. Cancer 1991;68:1932-6.
15. Zhu M, He Y, Baak JP, Zhou X, Qu Y, Sui L, et al. Factors that influence persistence or recurrence of high-grade squamous intraepithelial lesion with positive margins after the loop electrosurgical excision procedure: a retrospective study. BMC Cancer 2015;15:744.
16. Chen L, Liu L, Tao X, Guo L, Zhang H, Sui L. Risk Factor Analysis of Persistent High-Grade Squamous Intraepithelial Lesion After Loop Electrosurgical Excision Procedure Conization. J Low Genit Tract Dis 2019;23:24-7.
17. Hurtado-Roca Y, Becerra-Chauca N, Malca M. Efficacy and safety of cryotherapy, cold cone or thermocoagulation compared to LEEP as a therapy for cervical intraepithelial neoplasia: Systematic review. Rev Saude Publica 2020;54:27.
18. Mathevet P, Chemali E, Roy M, Dargent D. Long-term outcome of a randomized study comparing three techniques of conization: cold knife, laser, and LEEP. Eur J Obstet Gynecol Reprod Biol 2003;106:214-8.
19. Kyrgiou M, Athanasiou A, Paraskevaidi M, Mitra A, Kalliala I, Martin-Hirsch P, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. BMJ 2016;354:i3633.
20. Sasieni P, Castanon A, Landy R, Kyrgiou M, Kitchener H, Quigley M, et al. Risk of preterm birth following surgical treatment for cervical disease: executive summary of a recent symposium. BJOG 2016;123:1426-9.
21. Papoutsis D, Rodolakis A, Mesogitis S, Sotiropoulou M, Antsaklis A. Appropriate cone dimensions to achieve negative excision margins after large loop excision of transformation zone in the uterine cervix for cervical intraepithelial neoplasia. Gynecol Obstet Invest 2013;75:163-8.
22. Arbyn M, Redman CWE, Verdoodt F, Kyrgiou M, Tzafetas M, Ghaem-Maghami S, et al. Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis. Lancet Oncol 2017;18:1665-79.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:285-289
DOI: 10.4274/BMJ.galenos.2022.2022.3-11

Research

Relationship Between Successful Antitachycardic Pacing Delivery and ICD Device Settings

Başarılı Antitaşikardi Pacing Uyarımı ile ICD Cihaz Ayarları Arasındaki İlişki

Osman Pirhan, Abdülcelil Sait Ertuğrul

University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiac Electrophysiology, İstanbul, Turkey

ABSTRACT

Objective: The delivery of shock in patients with intracardiac defibrillators (ICD) devices is extremely inconvenient, and therefore it is desirable to terminate ventricular arrhythmias with antitachycardic pacing (ATP) as much as possible. In this study, we investigated the relationship between delivery of successful ATP and device measurement values.

Methods: A total of 31 patients were enrolled in the cross-sectional case-control study. Patients who were diagnosed with ATP or ICD shock therapy during pacemaker/lead control measurements performed in our outpatient clinic and patients who were admitted to our coronary intensive care unit due to appropriate ICD shock were included in the study. The patients were divided into two groups as those who successfully terminated ventricular tachycardia with ATP as the "successful ATP group" and those who did not terminate successful ventricular tachycardia with ATP as the "unsuccessful ATP group."

Results: In the correlation analysis performed between the demographic characteristics, clinical characteristics, battery and lead measurements of the patients and successful ATP, a statistically significant correlation was found between the mean ventricular tachycardia (VT) detection rate and the number of burst pacings and successful ATP (r= -0.699, p=0.036, and r= 0.414, p=0.036, respectively). Moreover, the presence of diabetes mellitus (DM) was significantly associated with successful ATP (r= -0.406 p=0.024). There was no significant relationship between other clinical and device measurement values and successful ATP.

Conclusion: Our study revealed that the presence of DM, the number of burst pacings, and the VT zone detection may be associated with ATP success in patients with ICD.

Keywords: Antitachycardic pacing, ventricular arrhythmias, shock delivery

ÖZ

Amaç: İntrakardiyak defibrilatör (ICD) cihazları olan hastalarda şok verilmesi son derece rahatsız edicidir ve bu nedenle ventriküler aritmilerin mümkün olduğunca antitaşikardik pacing (ATP) ile sonlandırılması arzu edilir. Bu çalışmada başarılı ATP verilmesi ile cihaz ölçüm değerleri arasındaki ilişkiyi araştırdık.

Gereç ve Yöntem: Kesitsel olgu kontrol çalışmasına toplam 31 hasta alındı. Polikliniğimizde yapılan kalp pili/lead kontrol ölçümlerinde ATP veya ICD şok tedavisi uygulanan hastalar ve uygun ICD şoku nedeniyle koroner yoğun bakım ünitemize başvuran hastalar çalışmaya dahil edildi. Hastalar ATP ile ventriküler taşikardiyi başarıyla sonlandıranlar "başarılı ATP grubu", ATP ile başarılı ventriküler taşikardiyi sonlandırmayanlar "başarısız ATP grubu" olarak iki gruba ayrıldı.

Bulgular: Hastaların demografik özellikleri, klinik özellikleri, pil ve lead ölçümleri ile başarılı ATP arasında yapılan korelasyon analizinde ortalama ventriküler taşikardi (VT) tespiti ve burst pacing sayısı ile başarılı ATP arasında istatistiksel olarak anlamlı korelasyon saptandı (r=-0,699, p=0,036 and r=0,414, p=0,036, sırasıyla). Ayrıca, diabetes mellitus (DM) varlığı başarılı ATP ile anlamlı olarak ilişkiliydi (r=-0,406 p=0,024). Diğer klinik ve cihaz ölçüm değerleri ile başarılı ATP arasında anlamlı bir ilişki yoktu.

Sonuç: Biz bu çalışmamızda, ICD'li hastalarda DM varlığının, burst pacing sayısının ve VT bölgesi tespitinin ATP başarısı ile ilişkili olabileceğini ortaya çıkardık.

Anahtar Kelimeler: Antitaşikardik uyarım, ventriküler aritmiler, şok uyarımı

Address for Correspondence: Osman Pirhan, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiac Electrophysiology, İstanbul, Turkey
Phone: +90 555 198 19 12 E-mail: opirhan@gmail.com ORCID ID: orcid.org/0000-0002-4977-3958

Cite as: Pirhan O, Ertuğrul AS. Relationship Between Successful Antitachycardic Pacing Delivery and ICD Device Settings. Med J Bakirkoy 2022;18:285-289

Received: 22.03.2022
Accepted: 23.06.2022

INTRODUCTION

Intracardiac defibrillators (ICDs) are recommended as a first-line treatment for treating malignant ventricular tachyarrhythmias due to the mortality benefit shown in comparative studies with medical treatment, particularly secondary prevention (1,2). The basic philosophy of these devices is to intervene in arrhythmia before hemodynamic deterioration and sudden cardiac arrest occur. ICDs attempt to restore the rhythm in ventricular tachycardias in two ways. Firstly, the devices attempt to terminate tachycardia by stimulation with a cycle length shorter than the detected cycle length, which is known as antitachycardic pacing (ATP). If this fails, secondly delivering shock according to the previously established treatment algorithms. The need for ICD shock is associated with a poor prognosis and is undesirable due to the negative effects of the shock itself (3). Therefore, it is critical to identify patients at high risk of ICD shock, develop patient-specific ICD programming algorithms, and avoid shocking by terminating arrhythmia with ATP (4,5). In this study, we investigated the relationship between ICDs' s ventricular lead measurement values and successful ATP or shock treatment.

METHODS

The Study Population

A total of 31 patients were enrolled in the cross-sectional case-control study conducted between September 2020 and November 2021. Patients who were diagnosed with ATP or ICD shock therapy during pacemaker/lead control measurements performed in our outpatient clinic and patients who were admitted to our coronary intensive care unit due to appropriate ICD shock were included in the study. The patients were divided into two groups as those who successfully terminated ventricular tachycardia with the ATP "successful ATP group," and those who did not terminate successful ventricular tachycardia with the ATP "unsuccessful ATP group." These two groups were compared in terms of demographic characteristics, clinical features, laboratory findings and ventricular lead measurement parameters. Patients with inappropriate shock, severe electrolyte imbalance, coronary artery stenosis requiring revascularization were excluded from the study. Written informed consent form was obtained from all patients who participated in the study, which was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2021-18-01, date: 20.09.2021).

Data Collection

Demographic characteristics, laboratory results, echocardiographic findings, pacemaker and lead measurements of all patients included in the study were recorded. Battery and lead measurements were obtained, pacemaker characteristics and the previously set ICD treatment algorithms were determined. Arrhythmia episodes were retrospectively analyzed and the number of arrhythmia attacks in the last 6 months and the rate of arrhythmia episodes requiring shock or terminated with ATP was determined.

Statistical Analysis

Normally distributed data are shown as mean ± standard deviation and non-normally distributed data are shown as median. The normality of the data was analyzed using the Shapiro-Wilk test. Independent sample t-test was used for parametric data and Mann-Whitney U test was used for nonparametric data in paired group comparison. Chi-square was used to compare categorical data. Spearman correlation analysis was used for the correlation analysis. Logistic regression was used to identify the predictors of successful ATP.

RESULTS

Of the 31 patients included in the study, 3 were women (9.7%) and the mean age of the patients was 61±11 years. The demographic characteristics of the patients, the drugs they use and the types of ICD are shown in Table 1. There was no statistically significant difference in terms of demographic characteristics, clinical features and type of ICD in the groups of patients with and without arrhythmia termination with successful ATP.

The results of pacemaker and right ventricular lead measurements analyzed in groups of patients whose ventricular tachycardias were terminated and who were not terminated with successful ATP are shown in Table 2. There was no statistically significant difference between the two groups in terms of the pacemaker measurement values obtained. The correlation relationship between successful ATP administration and demographic characteristics, clinical characteristics of the patients and the results of the analyzed pacemaker battery and right ventricular lead measurements is shown in Table 3. In the analysis of the correlation between the successful ATP group and the demographic characteristics, clinical characteristics, battery and lead measures of the patients, a statistically significant relationship was found between the average ventricular tachycardia (VT) detection rate (bpm) and the number of

Table 1. Comparison of successful ATP and unsuccessful ATP patient groups in terms of demographic characteristics, clinical features

	Successful ATP	Unsuccessful ATP	p-value
Age (years ± SD)	63.00±12.54	57.54±10.08	0.226
Gender n (%)			
Male	10 (35.7)	18 (64.3)	0.934
Female	1 (33.3)	2 (66.7)	-
HT	4 (36.4)	7 (63.6)	0.940
CAD	7 (33.3)	14 (66.7)	0.718
DM	5 (71.4)	2 (28.6)	0.067
CRF	1 (50)	1 (50)	1.00
HOCM	2 (100)	0 (0)	0.118
Congenital long QT syndrome	0 (0)	1 (100)	0.334
Beta blocker	11 (37.9)	18 (62.1)	0.527
ACEI/ARB	6 (33.3)	12 (66.7)	0.789
MRA	5 (38.5)	8 (6.5)	0.769
ARNI	0 (0)	1 (100)	0.344
Amiodarone	4 (44.4)	5 (55.6)	0.683
Digoxin	2 (66.7)	1 (33.3)	0.281
Ranolazine	0 (0)	1 (100)	0.344
Ivabradine	0 (0)	5 (100)	0.133
Loop diuretics	4 (40)	6 (60)	0.718
ICD type			
Single chamber	8 (44.4)	10 (55.6)	-
Dual chamber	2 (20)	8 (80)	0.413
CRT-D	1 (33.3)	2 (66.7)	-
EF (% ± SD)	32.50±14.06	37.09±16.70	0.343
LA diameter (mm ± SD)	42.11±5.79	42.72±10.25	0.837

ATP: Antitachycardic pacing, HT: Hypertension, CAD: Coronary artery disease, DM: Diabetes mellitus, HOCM: Hypertrophic obstructive cardiomyopathy, CRF: Chronic renal failure, ACEI/ARB: Angiotensin converting enzyme inhibitors/angiotensin receptor blockers, MRA: Mineralocorticoid receptor antagonists, ARNI: Angiotensin receptor-neprilysin inhibitor, ICD: Implantable cardioverter-defibrillator, EF: Ejection fraction, LA: Left atrium, CRT-D: Cardiac resynchronization therapy-defibrillator, SD: Standard deviation

burst pacings and successful ATP (r= -0.699, p=0.036, and r= 0.414, p=0.036, respectively). There was a statistically significant negative correlation between successful ATP and only diabetes mellitus (DM) (r= -0.406 p=0.024). There was no statistically significant correlation between other research parameters and successful ATP.

DISCUSSION

In this study, we found a statistically significant correlation between successful ATP and average VT detection rate, the number of burst pacings, and DM. To the best knowledge, our study is the first published study in the literature in this aspect.

ICD shock is an extremely unpleasant and painful condition for the patient and seriously affects the quality of life of patients. Additionally, anxiety disorders and increase in fear levels may also develop in patients with shock. Moreover, in the studies conducted, the expected life expectancy is also reduced in patients who experience ICD shock (6,7). Therefore, it is important to reduce the number of shocks in patients with ICD who develop severe ventricular arrhythmia and to terminate this rhythm disturbances with ATP as much as possible. According to the studies conducted on the subject, it is recommended a patient-specific device programming for terminating VT with successful ATP by reducing the number of ICD shocks (5,8,9). One of the

Table 2. Comparison of successful ATP and unsuccessful ATP patient groups in terms of pacemaker and right ventricular lead measurement

	Successful ATP	Unsuccessful ATP	p-value
Age (years)	63.00±12.54	57.54±10.08	0.226
HR (bpm)	77.00 (55-120)	68.50 (60-90)	0.769
Number of burst	3.0 (1-4)	1.0 (1-3)	0.075
Number of ramp	1.0 (0-3)	1.0 (0-2)	0.148
VT detection rate (bpm)	165.83±9.41	179.00±9.84	0.092
VF zone	200.00 (188-294)	200.00 (167-220)	0.338
VT zone	169.35±8.74	176.40±14.85	0.112
Number of episodes of arrhythmia	52.00 (2-800)	8.00 (1-249)	0.123
R wave (mV)	12.25±5.68	11.31±4.27	0.638
Impedance (Ω)	456.00(320-893)	447.00 (326-929)	0.855
Shock impedance (Ω)	57.27±11.24	57.27±11.24	0.542
Threshold (V)	0.75 (0.25-3.0)	0.75 (0.25-2.0)	1.00

ATP: Antitachycardic pacing, HR: Heart rate, VT: Ventricular tachycardia, VF: Ventricular fibrillation, Ω: Ohms

Table 3. The correlation relationship between successful ATP and demographic characteristics, clinical characteristics of the patients and the results of the analyzed pacemaker battery and right ventricular lead measurements

	R	p-value
HT	-0.014	0.942
DM	-0.406	0.024*
CAD	0.065	0.728
HOCM	-0.354	0.051
EF (%)	-0.149	0.424
LA (mm)	0.030	0.878
Threshold (V)	0.00	1.000
Shock impedance (Ω)	0.106	0.572
Impedance (Ω)	0.034	0.856
R wave (mV)	0.041	0.825
VF zone	0.194	0.295
VT zone	-0.140	0.460
VT detection	-0.699	0.036*
VT monitor	-0.069	0.840
Number of burst	0.414	0.036*
Number of ramp	0.327	0.103

*Correlation is significant at the 0.05 level (2-tailed)

ATP: Antitachycardic pacing, HT: Hypertension, CAD: Coronary artery disease, DM: Diabetes mellitus, HOCM: Hypertrophic obstructive cardiomyopathy, EF: Ejection fraction, LA: Left atrium, VT: Ventricular tachycardia, VF: Ventricular fibrillation, Ω: Ohms

important consequences of our study is that as the number of burst pacings increases in the device settings, it is more likely that malignant arrhythmia will be terminated with successful ATP. For this, the device must be programmed to perform burst pacing at least 3 times. Another result of our study is that the VT zone is unnecessarily high values, which can also reduce the chances of ATP success. Setting the VT zone to be around 165 bpm may be a more suitable programming option for successful ATP. Additionally, in our study, DM was found to be negative predictors of successive ATP. This result can be related to the that myocardial pathology and tachyarrhythmias are predominantly related to ischemic etiology in the diabetic population.

Our study has some limitations. Firstly, it was a small-scale and retrospective study. Moreover, there is an inability to reach the results of the ICD device brand and the patients' laboratory and coronary angiography on admission to the hospital.

CONCLUSION

Termination of fatal ventricular arrhythmias with ATP in patients with an ICD device should be the first choice of treatment and this issue has not been sufficiently investigated in the literature. In this study, we determined that the number of burst pacings and the VT zone value in the device settings may be related to ATP success. However, there is still a need for larger-scale and prospective studies on the subject.

ETHICS

Ethics Committee Approval: This study, with protocol number 2021/412, was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee decision no 2021-18-01 (date: 20.09.2021).

Informed Consent: Written informed consent form was obtained from all patients who participated in the study, which was approved by the regional ethics committee.

Authorship Contributions

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

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

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

REFERENCES

1. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med 1980;303:322-4.
2. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace 2015;17:1601-87.
3. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 2015;36:2793-867.
4. MacIntyre CJ, Sapp JL, Abdelwahab A, Al-Harbi M, Doucette S, Gray C, et al. The Effect of Shock Burden on Heart Failure and Mortality. CJC Open 2019;1:161-7.
5. Regoli F, Graf D, Schaer B, Duru F, Ammann P, Stefano LMDS, et al. Arrhythmic episodes in patients implanted with a cardioverter-defibrillator - results from the Prospective Study on Predictive Quality with Preferencing PainFree ATP therapies (4P). BMC Cardiovasc Disord 2019;19:146.
6. Wilkoff BL, Ousdigian KT, Sterns LD, Wang ZJ, Wilson RD, Morgan JM; EMPIRIC Trial Investigators. A comparison of empiric to physician-tailored programming of implantable cardioverter-defibrillators: results from the prospective randomized multicenter EMPIRIC trial. J Am Coll Cardiol 2006;48:330-9.
7. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, et al. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med 2008;359:1009-17.
8. Poole JE, Olshansky B, Mark DB, Anderson J, Johnson G, Hellkamp AS, et al. Long-Term Outcomes of Implantable Cardioverter-Defibrillator Therapy in the SCD-HeFT. J Am Coll Cardiol 2020;76:405-15.
9. Wilkoff BL, Williamson BD, Stern RS, Moore SL, Lu F, Lee SW, et al. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. J Am Coll Cardiol 2008;52:541-50.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:290-296
DOI: 10.4274/BMJ.galenos.2022.2022.3-15

Research

Comparison of the Use of Videolaryngoscopy and Direct Laryngoscopy Methods in Achieving Intubation Before Pediatric Cardiac Surgery

Pediatrik Kalp Cerrahisinde Videolaringoskopi ile Direkt Laringoskopi Uygulamalarının Karşılaştırılması

Hatice Dilek Özcanoğlu, Funda Gümüş Özcan

University of Health Sciences Turkey, Başakşehir Çam and Sakura Hospital, Clinic of Anaesthesiology and Reanimation, İstanbul, Turkey

ABSTRACT

Objective: Intubation is one of the essential components of preoperative airway management in the context of congenital heart surgery. Accordingly, it is aimed in this study was to compare the uses of direct laryngoscopy (DL) and videolaryngoscopy (VL) in achieving intubation in cases younger than two years of age who will undergo congenital heart surgery.

Methods: This study was conducted on patients younger than two years old who underwent congenital heart surgery in the hospital, where the study was conducted between September 1st, 2020, and April 1st, 2021. The cases included in this study were divided into two groups based on the method used to achieve intubation before the cardiac surgery, as the DL and VL groups. These groups were then compared in terms of hemodynamic parameters, difficulty, duration and number of intubation, Cormack-Lehane grades, and complications that developed in association with intubation. The results obtained were analyzed statistically.

Results: Each DL and VL group comprised 60 cases. The median age of the cases included in this study was four months (minimum one day & maximum 24 months). Fifty-three percent of the cases were male, and 47% were female. There was no significant difference between the groups in terms of gender, weight, presence of syndromes, presence of cyanotic heart disease, and frequency of redo cases ($p>0.05$). Systolic and diastolic arterial pressures were significantly higher ($p<0.05$), whereas the total intubation time was significantly shorter in the VL group compared to the DL group (21.5 and 30 seconds, respectively; $p<0.05$). There was no difference between the groups in terms of any need for intubation maneuver, the presence of backward, upward, rightward, pressure maneuver, the presence of (optimal external laryngeal manipulation), Cormack-Lehane grades, intubation attempts, and use of stylet ($p<0.05$). However, the desaturation period (0% vs. 13.1%) and aspiration requirement rate (13.3% vs. 41.7%) were lower in the VL group ($p<0.05$).

Conclusion: The findings of this study indicate that intubation can be achieved in a shorter time and with a similar complication rate with VL than with DL, thereby providing a better contribution to hemodynamics. Consequentially, the use of VL may be considered to achieve intubation in newborn and infant cases who will undergo congenital heart surgery.

Keywords: Pediatric, airway management, direct laryngoscopy, videolaryngoscopy, congenital heart surgery

ÖZ

Amaç: Bu çalışmada konjenital kalp cerrahisi operasyonu geçirecek iki yaşından küçük olgularda direkt laringoskopi (DL) ve videolaringoskopi (VL) ile entübasyon uygulamalarının etkilerinin karşılaştırılması amaçlandı.

Gereç ve Yöntem: Bu çalışma 1 Eylül 2020-1 Nisan 2021 tarihleri arasında hastanemizde konjenital kalp cerrahisi operasyonu geçiren iki yaşından küçük olgular üzerinde gerçekleştirildi. Olgular ameliyat öncesi entübasyon uygulama şekline göre DL ve VL olarak iki gruba ayrıldı. İşlemler hemodinamik parametreler, entübasyon zorluğu, süresi, sayısı, Cormack-Lehane skoru ve gelişen komplikasyonlar açısından karşılaştırıldı. Sonuçlar istatistiksel olarak değerlendirildi.

Bulgular: Çalışma döneminde her iki gruptan 60'şar olgu mevcuttu. Medyan yaş 4 ay (1 gün-24 ay) idi. Olguların %53'ü erkek ve %47'si kızdı. Grupların cinsiyet, ağırlık, sendrom varlığı, siyanotik kalp hastalığı varlığı, redo olgu sıklığı birbirine benzerdi ($p>0,05$).VL kullanılan olgularda

Address for Correspondence: Hatice Dilek Özcanoğlu, University of Health Sciences Turkey, Başakşehir Çam and Sakura Hospital, Clinic of Anaesthesiology and Reanimation, İstanbul, Turkey
Phone: +90 212 909 60 00 E-mail: dilekmersin@hotmail.com ORCID ID: orcid.org/0000-0001-8091-9997

Cite as: Özcanoğlu HD, Gümüş Özcan F. Comparison of the Use of Videolaryngoscopy and Direct Laryngoscopy Methods in Achieving Intubation Before Pediatric Cardiac Surgery. Med J Bakirkoy 2022;18:290-296

Received: 25.03.2022
Accepted: 23.06.2022

sistolik ve diyastolik arter basıncı daha yüksekti (p<0,05). Total entübasyon süresi VL grubunda DL grubuna göre daha kısaydı (21,5 vs 30 saniye, p<0,05). Gruplar arasında entübasyon manevra ihtiyacı, arka, yukarı ve sağa doğru basınç manevra varlığı, optimal dış laringeal manipülasyon varlığı, Cormack Lehane skoru, entübasyon denemesi, stile kullanımı arasında fark yoktu (p>0,05). VL grubunda desatürasyon süresi periyodu (%0 vs %13,1) ve aspirasyon ihtiyacı oranı(%13,3 vs %41,7) daha düşük oranda görüldü (p<0,05).

Sonuç: VL kullanımı ile DL kullanımına göre benzer komplikasyon oranında daha kısa sürede entübasyon gerçekleştirilerek hemodinamiye daha iyi katkı sağlanabilir. Bu nedenle artan deneyim ile ilişkili olarak konjenital kalp cerrahisi uygulanacak yenidoğan ve infant olgularda entübasyonda VL kullanımı düşünülebilir.

Anahtar Kelimeler: Çocuk, hava yolu yönetimi, direkt laringoskopi, videolaringoskop, konjenital kalp cerrahisi

INTRODUCTION

Airway management in children presents many challenges for pediatricians and anesthetists. The airway anatomy of children is different from that of adults. The upper location of the larynx, a relatively larger tongue, and a more limited mouth opening create difficulties for laryngoscopy and intubation (1,2). An adequate visualization of the airway and associated structures are required for successful intubation. In this way, prolonged or repeat intubation attempts would also be prevented to a large extent (3). First-pass success in tracheal intubation is particularly important in these patients because repeated intubation attempts can lead to airway trauma, increased obstruction, and hypoxemia, which can lead to potentially fatal outcomes (4,5).

It is crucial to perform fast, safe, and less traumatic intubation in infants with low or borderline oxygen saturation due to cardiac pathology who will undergo cardiac surgery. In this respect, the use of videolaryngoscopy (VL) in pediatric patients, which is more commonly used in adults, is increasingly recommended in airway management guidelines considering its efficiency in facilitating tracheal intubation (6,7). VL involves the use of video imaging and optical technology to facilitate indirect visualization of the larynx during intubation and is of evolutionary importance in intubation technology. Its use in pediatric patients has become prominent in the last 5-10 years in particular (1,8). However, extensive clinical studies on the efficacy of VL in routine daily practice or in children with difficult airways are scarce and inconclusive (9,10).

In view of the foregoing, it is aimed in this study to compare the uses of direct laryngoscopy (DL) and VL to achieve endotracheal intubation in pediatric patients aged 0-2 years who had undergone congenital heart surgery in terms of the effects thereof on hemodynamics, Cormack-Lehane image grades, total intubation times, maneuver needs, and complication rates.

METHODS

Our medical data about patients were recorded prospectively in to the anesthesiology clinical database. All patients agreed to participate in the study and written informed consent was obtained from each participant. The study was planned in accordance with the Declaration of Helsinki after obtaining the required approval from the local ethics committee (University of Health Sciences Turkey, Başakşehir Çam and Sakura Hospital - no: 2021.04.72). After gathering ethical committee approval, the data which were recorded in the database, about patients younger than two years old who underwent congenital heart surgery in the hospital, between September 1st, 2020, and April 1st, 2021 was taken out and analyzed. Patients who were over the age of two at the time of intubation, brought to the operating room from the intensive care unit as already intubated or resuscitated, and whose records could not be reached were excluded from the study. Patients included in this study were divided into two groups based on the method used to achieve intubation before the cardiac surgery, as the DL and VL groups. A patient information form that includes demographic, clinical, and hemodynamic characteristics of the patients, i.e., age, gender, weight, presence of syndromes, presence of redo and intubation information, etc. was created, and filled out for each patient. Patients whose oral intake was discontinued in accordance with the guidelines, that is, solid food, breast milk, and clear liquid intake were discontinued 6 h, 4 h, and 2 h before the procedure, respectively, were monitored by electrocardiography, pulse oximetry, non-invasive blood pressure measurement, and near-infrared spectrometry after they were brought into the operating room. After that, patients with intravenous access were administered 0.05 mg/kg midazolam for premedication. Mask ventilation was started after the administration of 1 mg/kg ketamine, 1 µg/kg fentanyl, and 0.1 mg/kg rocuronium in anesthesia induction. Orotracheal intubation was performed after two minutes of mask ventilation. A conventional laryngoscope [size 0 to 2 Macintosh and Miller blades (Heine Optotechnik, Munich, Germany)] was used in the DL group. A C-MAC videolaryngoscope [endolarynx videolaryngoscope size 0 to 2 Macintosh and Miller blades, 3 inch liquid crystal display screen, viewing angle above 60 degrees, front-to-back rotation angle 0-130 degrees, 225 gr, USB memory (Karl Storz GmbH, Tuttlingen, Germany)] was used in the VL group.

Patients' pre- and post-intubation pulse rates, systolic and diastolic arterial pressures, and SpO_2 levels were recorded. The time from the insertion of a blade into the mouth till monitoring the end-tidal carbon dioxide on the screen was recorded as the total intubation time. Along with the intubation time, the number of intubation attempts, the need for BURP (backward, upward, right, pressure) maneuver, the need for OELM (optimal external laryngeal manipulation), the Cormack-Lehane grades, the need for stylet and aspiration, the need for tube replacement due to post-intubation leakage, whether the tube number used was cuffed, and complications such as difficult intubation during the procedure, the presence of desaturation, esophageal intubation, oral and dental mucosal injury was recorded in the patient information form. The results obtained were analyzed statistically both within and between the groups.

Statistical Analysis

The descriptive statistics used to summarize the research data were tabulated using mean ± standard deviation or median, minimum and maximum values in case of continuous (numerical) variables, depending on whether they conform to the normal distribution, and as numbers and percentages in case of categorical variables. Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to check whether the numerical variables conformed to the normal distribution. In the comparative analysis of two independent groups; the independent samples t-test was used for cases when numerical variables were determined to conform to the normal distribution, and the Mann-Whitney U test was used for cases when numerical variables were determined not to conform to the normal distribution. In the comparative analysis of the differences between categorical variables per the group; Pearson's chi-square test was used in the case of 2x2 tables, which are expected to have 5 or more cells, Fisher's Exact test was used in the case of 2x2 tables, which are expected to have less than 5 cells, and Fisher-Freeman-Halton Exact test was used in the case of RxC tables, which are expected to have less than 5 cells. Statistical analysis were performed using the Jamovi project (2020) version 2.0.0.0 computer software (retrieved from https://www.jamovi.org) and JASP version 0.14.1.0 software (retrieved from https://jasp-stats.org). Probability (p) values calculated as <0.05 in statistical analyses were deemed to be statistically significant.

RESULTS

Each DL and VL group comprised 60 cases. The median age of the cases included in this study was 4 months (minium 1 day & maximum 24 months). Fifty-six (46.7%) cases were female, and 64 (53.3%) were male. Sixty-six (55.0%) of the cases had cyanotic congenital heart disease (CHD). A genetic syndrome was detected in 36 (30.0%) cases. Forty-five (37.5%) cases had a difficult intubation, and 69 (57.5%) cases required intubation maneuvers. BURP and OELM maneuvers were performed in 59 (49.2%) and 68 (56.7%) cases, respectively. The demographic characteristics of the groups are shown in Table 1. In terms of Cormack-Lehane grading, 33 (27.5%) cases were grade 1, 55 (45.8%) cases were grade 2, 25 (20.8%) cases were grade 3, and 7 (5.8%) cases were grade 4. There was no significant difference between the groups in Cormack-Lehane grades (p=0.232). A stylet was required in 20 (16.7%) of the cases. The aspiration was required in 33 (27.5%) cases. The need for aspiration was significantly higher in the DL group than the VL group (41.7% vs. 13.3%, p=0.001). However, no significant difference was found between the groups in terms of intubation tube replacement, post-intubation leakage, esophageal intubation rates, intubation tube number, or the number of intubation attempts (p>0.05). The desaturation period was significantly longer in the DL group than in the VL group (11.7% vs. 0%, p=0.013). Additionally, total intubation time was significantly longer in the DL group (30.0 seconds; 15.0-60.0) than in the VL group (21.5 seconds; 7.0-100.0) (p=0.016). The clinical characteristics of the groups are shown in Table 2.

Pre- and post-intubation systolic blood pressures of the patients who underwent DL were significantly lower than the patients who underwent VL [83.4 mmHg±19.1 mmHg vs. 101.1 mmHg±18.9 mmHg (p<0.001), 92.2 mmHg±17.6 mmHg vs. 106.1 mmHg±21.6 mmHg (p<0.001), respectively]. In parallel, pre- and post-intubation diastolic blood pressures of the patients who underwent DL were significantly lower than the patients who underwent VL [43.7 mmHg±13.1 mmHg vs. 59.3 mmHg±17.3 mmHg (p<0.001), 50.1 mmHg±13.0 mmHg vs. 65.3 mmHg±15.8 mmHg (p>0.001), respectively].

There was no significant difference between the groups in terms of peripheral oxygen saturation (SpO_2) levels (p=0.267). Post-intubation SpO_2 levels were significantly higher in the VL group (99.0; 82.0-100.0) than in the DL group (98.0; 72.0-100.0) (p=0.040). However, there was no significant difference between the groups in terms of pre- and post-intubation pulse rates (p=0.187 and p=0.404, respectively). The hemodynamic characteristics of the groups are shown in Table 3.

DISCUSSION

This study is one of the few studies that compared the uses of DL and VL to achieve endotracheal intubation in pediatric patients aged 0-2 years in the American Society

Table 1. Comparison of sociodemographic, clinical and hemodynamic characteristics of patients who underwent DL and VL

		Group		p-value
	Total (n=120)	DL (n=60)	VL (n=60)	
Age	4.0 (0.0-24.0)	4.0 (0.0-24.0)	5.5 (0.0-24.0)	0.317**
Gender				
Female	56 (46.7)	25 (41.7)	31 (51.7)	0.360***
Male	64 (53.3)	35 (58.3)	29 (48.3)	
Weight (kg)	5.8±2.4	5.4±2.2	6.0±2.4	0.058*
Height (cm)	60.7±11.3	59.6±12.2	61.9±10.0	0.098*
Redo (yes)	7 (5.8)	4 (6.7)	3 (5.0)	0.999***
Cyanotic heart disease (yes)	66 (55.0)	30 (50.0)	36 (60.0)	0.359***
Syndrome (yes)	36 (30.0)	21 (35.0)	15 (25.0)	0.319***
Type of syndrome				
Down	22 (61.1)	13 (61.9)	9 (60.0)	0.219***
George	2 (5.6)	0 (0.0)	2 (13.3)	
Other	12 (33.3)	8 (38.1)	4 (26.7)	
Difficult intubation (yes)	45 (37.5)	22 (36.7)	23 (38.3)	0.999***
Video (yes)	60 (50.0)	0 (0.0)	60 (100.0)	<0.001***
Video blade type (yes)	108 (90.0)	57 (95.0)	51 (85.0)	0.128***
Video blade size number				
N. 1	31 (25.8)	9 (15.0)	22 (36.7)	0.004***
N. 2	81 (67.5)	44 (73.3)	37 (61.7)	
N. 3	8 (6.7)	7 (11.7)	1 (1.7)	
Need for intubation maneuver (yes)	69 (57.5)	33 (55.0)	36 (60.0)	0.712***
BURP (yes)	59 (49.2)	27 (45.0)	32 (53.3)	0.465***
OELM (yes)	68 (56.7)	31 (51.7)	37 (61.7)	0.357***
Hyperextension (yes)	44 (36.7)	30 (50.0)	14 (23.3)	0.004***

*Independent sample t-test, **Mann-Whitney U test, ***Pearson's chi-squared test/Fisher's Exact test/Fisher-Freeman-Halton Exact test, DL: Direct laryngoscopy; VL: Videolaryngoscopy, BURP: Backward, upward, rightward, pressure, OELM: Optimal external laryngeal manipulation

of Anesthesiology III-IV group who had undergone congenital heart surgery, in terms of the effects thereof on hemodynamics, Cormack-Lehane image grades, total intubation times, maneuver requirements, and complication rates associated with the intubation procedure. Consequentially, it was found that the use of VL shortened the intubation time and had a significant positive effect on hemodynamics by ensuring higher systolic and diastolic arterial pressures.

CHDs are a group of diseases that feature with different pathologies, and are observed in 4-8 cases per 1,000 cases of live birth. It is crucial to be careful during the intubation phase in this pediatric patients population due to reasons such as insufficient cardiopulmonary reserve, presence of craniofacial anomalies, and complexity of the anatomical airways. Despite the newly developed equipment and evidence in pediatric airway management, DL remains the primary method used in achieving intubation. Nevertheless, difficult airways, in particular, have a negative effect on mortality and morbidity in pediatric patients with CHD, and in this context, there has been an increase in the use of VL recently, mainly due to the Coronavirus disease-2019 (COVID-19) pandemic and the adverse effects of DL in cases with difficult airways. However, not enough studies demonstrate the advantages of VL over DL in the management of difficult airways in pediatric patients with CHD. In the few studies available in the literature, the effects of DL and VL were compared, and various suggestions have

Table 2. Comparison of clinical characteristics of patients who underwent DL and VL

	Group			p-value
	Total (s=120)	DL (s=60)	VL (s=60)	
Cormack-Lehane grade				
Grade 1	33 (27.5)	19 (31.7)	14 (23.3)	0.232**
Grade 2	55 (45.8)	30 (50.0)	25 (41.7)	
Grade 3	25 (20.8)	9 (15.0)	16 (26.7)	
Grade 4	7 (5.8)	2 (3.3)	5 (8.3)	
Need for stylet (yes)	20 (16.7)	11 (18.3)	9 (15.0)	0.806**
Need for aspiration (yes)	33 (27.5)	25 (41.7)	8 (13.3)	0.001**
Intubation tube replacement (yes)	16 (13.3)	10 (16.7)	6 (10.0)	0.420**
Post-intubation leakage (yes)	11 (9.2)	8 (13.3)	3 (5.0)	0.206**
Esophageal intubation (yes)	3 (2.5)	3 (5.0)	0 (0.0)	0.244**
Desaturation period (yes)	7 (5.8)	7 (11.7)	0 (0.0)	0.013**
Bradycardia (yes)	7 (5.8)	5 (8.3)	2 (3.3)	0.439**
Intubation tube n (%)				
N. 3	5 (4.2)	4 (6.7)	1 (1.7)	0.172**
N. 3. 5	56 (46.7)	32 (53.3)	24 (40.0)	
N. 4	43 (35.8)	19 (31.7)	24 (40.0)	
N. 4. 5	14 (11.7)	5 (8.3)	9 (15.0)	
N. 5	2 (1.7)	0 (0.0)	2 (3.3)	
Cuffed intubation tube (yes)	94 (78.3)	39 (65.0)	55 (91.7)	0.001**
Difficult intubation during practice (yes)	23 (19.2)	12 (20.0)	11 (18.3)	0.999**
Total number of attempts	1.0 (1.0-5.0)	1.0 (1.0-5.0)	1.0 (1.0-3.0)	0.466*
Total intubation times	25.0 (7.0-100.0)	30.0 (15.0-60.0)	21.5 (7.0-100.0)	0.016*

*Mann-Whitney U test, **Pearson's chi-squared test/Fisher's Exact test/Fisher-Freeman-Halton Exact test, DL: Direct laryngoscopy; VL: Videolaryngoscopy

been made (9-11). To give a few examples; Riveros et al. (12) asserted that VL has no direct advantage over DL in pediatric cases ranging from newborns to cases of ten years of age and that its use should be limited to difficult airways; Hajiyeva et al. (13) concluded as a result of their study conducted with 56 pediatric patients aged 5-10 years who underwent elective surgery that VL is a good alternative for DL in routine and difficult intubation; and in another study (14) including training of anesthesia assistants and anesthesia technicians using a 3-6 month-old Pierre Robin syndrome dummy, VL was found to be more advantageous over DL, as it provides a good glottic view and required less number of attempts. In comparison, in this study, VL was found to be more advantageous over DL in the patient group with CHD as it provided an excellent glottic view, required a lesser number of attempts and did not result in any complications. Javaherforooshzadeh and Gharacheh (11) reported as a result of their study, including 60 pediatric cases, that the total intubation time was significantly lower in the DL group than in the VL group (51.13±17.88 seconds vs. 59.66±45.91 seconds, p=0.006), the rates of the first three attempts was comparable, and the rate was significantly less in the VL group after the third attempt. Fiadjoe et al. (4) reported as a result of their study, including cases with typical normal airway anatomy, that VL resulted in a longer total intubation time than DL (22.6 seconds vs. 21.4 seconds), yet provided a better and faster glottis vision for intubation. Lastly, Sinha et al. (15) did not find any significant difference between the DL and VL groups in terms of intubation times (24.80±7.90 vs. 27.90±10.90 seconds) in pediatric cases aged 4-14 years. In comparison, in this study, the total intubation time was found to be significantly lower in the VL group than in the DL group (21.5 seconds vs. 30 seconds, p=0.016). The discrepancy between the respective results of this study

Table 3. Comparison of vital signs (hemodynamic characteristics) patients who underwent DL and VL

		Group		p-value*
	Total (n=120)	DL (n=60)	VL (n=60)	
SBP				
Pre-intubation	92.3±20.9	83.4±19.1	101.1±18.9	<0.001
Post-intubation	99.2±20.8	92.2±17.6	106.1±21.6	<0.001
p-value**	-	<0.001	0.007	
DBP				
Pre-intubation	51.5±17.2	43.7±13.1	59.3±17.3	<0.001
Post-intubation	57.7±16.3	50.1±13.0	65.3±15.8	<0.001
p-value**	-	<0.001	0.003	
SpO_2				
Pre-intubation	91.0 (50.0-100.0)	93.5 (56.0-100.0)	90.0 (50.0-100.0)	0.267
Post-intubation	99.0 (72.0-100.0)	98.0 (72.0-100.0)	99.0 (82.0-100.0)	0.060
p-value **	-	<0.001	<0.001	
Pulse rate				
Pre-intubation	135.8±16.5	133.8±15.9	137.8±16.9	0.187
Post-intubation	144.0±14.9	142.8±12.6	145.1±16.9	0.404
p-value **	-	<0.001	<0.001	

*Independent samples t-test/Mann-Whitney U test, **Paired-sample t-test/Wilcoxon test, DL: Direct laryngoscopy, VL: Videolaryngoscopy, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SpO_2: Peripheral oxygen saturation

and the results of the comparable studies with respect of the total intubation time can be attributed to the increase in the experience of pediatric anesthesiologists over the years, and particularly to the fact that VL has become part of daily practice along with the COVID-19 pandemic. The blade type used in DL and VL has been reported to have affected the intubation success and complication rates (9-13). In this study, in parallel with the studies reported in the literature, three of the size 0 to 2 MAC 57 Miller type blades were used in the DL group, and nine of the size 0 to 2 MAC 51 Miller type blades were used in the VL group. A higher number of size 1 blades were used in the VL group than in the DL group. The differences between the groups in terms of types of blades used were attributed to the differences in the physical structures of the patients. Working principles of different types of VL are the same, yet they differ in terms of screen placement, different blade types, blades with different size numbers, and endotracheal tube placement strategies (10). GlideScope, Storz DCI, Bonfils, C-MAC, Truview PCD pediatric, Airtraq, McGrath series 5 are among the VL types that can be used in pediatric airway (9). Given its design similar to DLs, C-MAC VL has been recommended as the most suitable models for use by anesthesiologists, particularly in the pediatric patient population (8). In line with this recommendation, C-MAC VL was used in this study. Endotracheal intubation in pediatric patients requires different maneuvers due to the varying characteristics of the airway, and the associated complications also differ from case to case (7-11). In a study involving 60 cases diagnosed with CHD, 40%, 40%, and 20% of the DL cases were graded as grade 1, grade 2, and grade 3 as per the Cormack-Lehane grading system, respectively, and none (0%) was graded as grade 4. In comparison, 73% and 27% of the VL cases were graded as grade 1 and grade 2 as per the Cormack-Lehane grading system, respectively, and none (0%) was graded as grade 3 or grade 4 (11). In comparison, in this study, 32%, 50%, 15%, and 3% of the DL cases were graded as grade 1, grade 2, grade 3, and grade 4 as per Cormack-Lehane grading system, respectively, whereas 23%, 42%, 28%, and 8% of the VL cases were graded as grade 1, grade 2, grade 3, and grade 4 as per Cormack-Lehane grading system, respectively. Accordingly, there was no significant difference between the groups in terms of Cormack-Lehane grades. The rates of the associated complications were also found to be similar to the respective results reported in the literature. Significant hemodynamic changes may develop during intubation. For example, pulse rate may increase due to catecholamine discharge that occurs following intubation

and laryngoscopy (16). In their study involving adult cases, Maassen et al. (17) found that the increase in pulse rate and systolic blood pressure in the VL group was significantly less than in the DL group. In another study, significantly higher pulse rates and lower SpO_2 levels were reported in the VL group compared to the DL group ($p<0.05$) (11). In comparison, in this study, significant hemodynamic changes were observed following intubation in both the DL and VL groups, which were manifested as increases in systolic blood pressure, diastolic blood pressure, peripheral oxygen saturation, and pulse rate. Systolic and diastolic blood pressures and pulse rate was significantly higher in VL than in DL. This difference was attributed to low cardiac reserves of congenital heart patients and low VL intubation times.

The main limitations of this study are that it was conducted as a single-center study and with a relatively limited number of patients.

CONCLUSION

It has been concluded because of this study that VL can be used safely in routine anesthesia practice in the pediatric population of 0-2 age group with CHD, which is a risky patient population, by experienced specialists and with suitable equipment. Additionally, the findings of this study indicate that intubation can be achieved in a shorter time with VL compared to DL, with an excellent glottic appearance, without the need for auxiliary intubation maneuvers and any increase in the associated complications. Large-scale case series are needed to corroborate the results of this study.

ETHICS

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura Hospital Ethics Committee (no: 2021.04.72).

Informed Consent: All patients agreed to participate in the study and written informed consent was obtained from each participant.

Authorship Contributions

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

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

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

REFERENCES

1. Fiadjoe JE, Kovatsis P. Videolaryngoscopes in pediatric anesthesia: what's new? Minerva Anestesiol 2014;80:76-82.
2. Sun Y, Lu Y, Huang Y, Jiang H. Pediatric video laryngoscope versus direct laryngoscope: a meta-analysis of randomized controlled trials. Paediatr Anaesth 2014;24:1056-65.
3. Lingappan K, Arnold JL, Fernandes CJ, Pammi M. Videolaryngoscopy versus direct laryngoscopy for tracheal intubation in neonates. Cochrane Database Syst Rev 2018;6:CD009975.
4. Fiadjoe JE, Nishisaki A, Jagannathan N, Hunyady AI, Greenberg RS, Reynolds PI, et al. Airway management complications in children with difficult tracheal intubation from the Pediatric Difficult Intubation (PeDI) registry: a prospective cohort analysis. Lancet Respir Med 2016;4:37-48.
5. Hippard HK, Kalyani G, Olutoye OA, Mann DG, Watcha MF. A comparison of the Truview PCD and the GlideScope Cobalt AVL video-laryngoscopes to the Miller blade for successfully intubating manikins simulating normal and difficult pediatric airways. Paediatr Anaesth 2016;26:613-20.
6. Higgs A, McGrath BA, Goddard C, Rangasami J, Suntharalingam G, Gale R, et al. Guidelines for the management of tracheal intubation in critically ill adults. Br J Anaesth 2018;120:323-52.
7. Downey AW, Duggan LV, Adam Law J. A systematic review of meta-analyses comparing direct laryngoscopy with videolaryngoscopy. Can J Anaesth 2021;68:706-14.
8. Xue FS, Liu YY, Li HX, Yang GZ. Paediatric video laryngoscopy and airway management: What's the clinical evidence? Anaesth Crit Care Pain Med 2018;37:459-66.
9. Wallace C, Engelhardt T. Videolaryngoscopes in Paediatric Anaesthesia. Current Treatment Options in Pediatrics 2015;1:25-37.
10. Balaban O, Tobias JD. Videolaryngoscopy in Neonates, Infants, and Children. Pediatr Crit Care Med 2017;18:477-85.
11. Javaherforooshzadeh F, Gharacheh L. The Comparison of Direct Laryngoscopy and Video Laryngoscopy in Pediatric Airways Management for Congenital Heart Surgery: A Randomized Clinical Trial. Anesth Pain Med 2020;10:e99827.
12. Riveros R, Sung W, Sessler DI, Sanchez IP, Mendoza ML, Mascha EJ, et al. Comparison of the Truview PCD™ and the GlideScope(®) video laryngoscopes with direct laryngoscopy in pediatric patients: a randomized trial. Can J Anaesth 2013;60:450-7.
13. Hajiyeva K, Can ÖS, Baytaş V, Yıldırım Güçlü Ç. Comparison of the C-MAC D-Blade videolaryngoscope and direct laryngoscope in pediatric patients: Randomized controlled trial. Ulus Travma Acil Cerrahi Derg 2021;27:421-6.
14. Saracoglu KT, Eti Z, Kavas AD, Umuroglu T. Straight video blades are advantageous than curved blades in simulated pediatric difficult intubation. Paediatr Anaesth 2014;24:297-302.
15. Sinha R, Sharma A, Ray BR, Kumar Pandey R, Darlong V, Punj J, et al. Comparison of the Success of Two Techniques for the Endotracheal Intubation with C-MAC Video Laryngoscope Miller Blade in Children: A Prospective Randomized Study. Anesthesiol Res Pract 2016;2016:4196813.
16. Abdelgawad AF, Shi QF, Halawa MA, Wu ZL, Wu ZY, Chen XD, et al. Comparison of cardiac output and hemodynamic responses of intubation among different videolaryngoscopies in normotensive and hypertensive patients. J Huazhong Univ Sci Technolog Med Sci 2015;35:432-8.
17. Maassen RL, Pieters BM, Maathuis B, Serroyen J, Marcus MA, Wouters P, et al. Endotracheal intubation using videolaryngoscopy causes less cardiovascular response compared to classic direct laryngoscopy, in cardiac patients according a standard hospital protocol. Acta Anaesthesiol Belg 2012;63:181-6.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:297-302
DOI: 10.4274/BMJ.galenos.2022.2022.2-5

Research

Prognostic Significance of Soluble CD163 in Hospitalized Patients with COVID-19

COVİD-19 ile Yatırılan Hastalarda Soluble CD163'ün Prognostik Önemi

Ahmet Nalbant[1], Tezcan Kaya[1], Selçuk Yaylacı[1], Deniz Çekiç[2], Kezban Süner[3], Cengiz Karacaer[2], Erdem Çokluk[4], Cahit Bilgin[5]

[1]Sakarya University Faculty of Medicine, Department of Internal Medicine, Sakarya, Turkey
[2]Sakarya University Training and Research Hospital, Clinic of Internal Medicine, Sakarya, Turkey
[3]Sakarya University Training and Research Hospital, Clinic of Intensive Care Unit, Sakarya, Turkey
[4]Sakarya University Faculty of Medicine, Department of Biochemistry, Sakarya, Turkey
[5]Sakarya University Faculty of Medicine, Department of Chest Diseases, Sakarya, Turkey

ABSTRACT

Objective: Soluble CD163 (sCD163) is a biomarker involved in inflammation. There is little data on the prognostic utility of sCD163 in coronavirus disease-2019 (COVID-19). This study investigated the relationship between serum sCD163 and the prognosis of COVID-19.

Methods: A total of 79 hospitalized patients diagnosed with COVID-19 were included in this retrospective study. Patients were divided into two groups as survivors and non-survivors. The clinical characteristics, serum sCD163 level, and other laboratory data of patients were compared between the groups.

Results: Forty-two (53.2%) of the 79 cases were male. The mean age was 70.4±12 years in the non-survivor group and 64.2±14 years in the survivor group (p=0.079). Serum sCD163, prothrombin time, and lactate were significantly higher in non-survivors than in survivors (p=0.023, p=0.015, p=0.018, respectively). The optimum cutoff value of serum sCD163 by receiver operating curve analysis was 2.92 ng/mL, resulting in 74% sensitivity and 52% specificity for predicting mortality (area under the curve: 0.620, 95% confidence interval: 0.481-0.759, p=0.048). Serum sCD163≥2.92 ng/mL was associated with 4.3 times higher mortality risk as assessed by logistic regression analysis (p=0.014).

Conclusion: sCD163 is an independent predictor of mortality in COVID-19 positive patients who have a fatal course of the disease.

Keywords: Soluble CD163, COVID-19, inflammation, mortality

ÖZ

Amaç: Suluble CD163 (sCD163) enflamasyonla ilgili biyobelirteçlerinden biridir. Koronavirüs hastalığı-2019'da (COVİD-19) sCD163'ün prognostik faydası hakkında çok az veri var. Bu çalışma sCD163 seviyeleri ve hastalığın prognozu arasında ilişki olup olmadığının araştırılmasını amaçladı.

Gereç ve Yöntem: Bu retrospektif çalışmaya COVİD-19 tanısı konan toplam 79 hastanede yatan hasta dahil edildi. Hastalar sağ kalanlar ve sağ kalmayanlar olarak iki gruba ayrıldı. Hastaların klinik özellikleri, serum sCD163 düzeyi ve diğer laboratuvar verileri gruplar arasında karşılaştırıldı.

Bulgular: Yetmiş dokuz olgunun 42'si (%53,2) erkek idi. Hayatta olmayan grupta yaş ortalaması 70,4±12 yıl ve hayatta olan grupta 64,2±14 yıl saptandı (p=0,079). Hayatta olmayanlarda sCD163, protrombin zamanı ve laktat düzeyleri hayatta olanlara göre istatistiksel olarak anlamlı yüksek bulundu sırasıyla (p=0,023, p=0,015, p=0,018). Hayatta olmayan grupta alıcı çalışma karakteristik analizi yapıldığında sCD163≥2,92 olduğunda eğrinin altındaki alan (AUC) değeri (AUC: 0,620, %95 güven aralığı: 0,481-0,759, p=0,048), sensitivitesi %74, spesifitesi %52 bulundu. Lojistik regresyon analizinde sCD163≥2,92 olduğunda mortalite riski 4,3 kat daha fazla olarak saptandı (p=0,014).

Sonuç: sCD163 ölümcül seyri olan COVİD-19 pozitif hastalarda mortalitenin bağımsız bir öngördürücüsüdür.

Anahtar Kelimeler: Soluble CD163, COVİD-19, enflamasyon, mortalite

Address for Correspondence: Ahmet Nalbant, Sakarya University Faculty of Medicine, Department of Internal Medicine, Sakarya, Turkey
Phone: +90 264 888 4001 E-mail: drnalbant@hotmail.com ORCID ID: orcid.org/0000-0003-4756-3575

Cite as: Nalbant A, Kaya T, Yaylacı S, Çekiç D, Süner K, Karacaer C, Çokluk E, Bilgin C. Prognostic Significance of Soluble CD163 in Hospitalized Patients with COVID-19. Med J Bakirkoy 2022;18:297-302

Received: 09.02.2022
Accepted: 24.06.2022

INTRODUCTION

Coronavirus disease-2019 (COVID-19) worldwide is an infection caused by the respiratory syndrome coronavirus-2 (1). The effects of COVID-19 may be different clinical pictures, from an asymptomatic carrier ship to respiratory system findings such as fever, sore throat, shortness of breath, cough and bilateral pneumonic infiltration, and acute respiratory distress syndrome. Cases presenting findings such as abdominal pain, headache, diarrhea, smell and taste disorders, and skin lesions have also been reported (2). Death generally occurs in older people or individuals with accompanying systemic diseases (hypertension, diabetes mellitus, chronic lung diseases, cardiovascular disease, and cancer) (3). Soluble CD163 (sCD163) has been described as a cell surface molecule, which is a member of the scavenger receptor cysteine-rich superfamily, that is present in particular on the surface of monocytes and macrophages as a haptoglobin-hemoglobin receptor (4). A soluble form of CD163 ectodomain is present in normal plasma comprising at least 94% of all CD163 and binds haptoglobin-hemoglobin complexes (5). The known most potent known stimulators of sCD163 expression are glucocorticoids, interleukin (IL)-6, IL-10, and heme/hemoglobin (6). sCD163 has a weak apoptosis inducer similar to tumor necrosis factor-α (7), and viruses (8). sCD163 may play an essential role in resolving inflammation (9). sCD163 is an indicator for the activation of macrophages and is increased in macrophage activation syndrome (10). Macrophages expressing CD163 have been detected in the vicinity of chronically inflamed joints (11), and tumor cells (tumor-associated macrophages) (12). sCD163 has been associated with disease progression in viral hepatitis B and C (13), increased mortality after sepsis (14), and stenosis and coronary lesions in human immunodeficiency virus (HIV)-infected individuals (15). COVID-19 is a novel disease, and it has been found in the literature that many pro-inflammatory cytokines and other acute-phase reactants correlate with a poor prognosis of the disease (16). However, there are no specific biomarkers for the prognosis and survival of COVID-19. There are limited data on the prognostic utility of sCD163 in COVID-19. This study investigated the relationship between serum sCD163 and the prognosis of COVID-19.

METHODS

A total of 79 patients who had were hospitalized [in intensive care unit (ICU) and in non-ICU)] between 01.09.2020 and 31.10.2020. Patients over the age of 18 who were positive for COVID-19 were included in the study. All data of the patients were obtained retrospectively. Patients were divided into two groups as survivors and non-survivors. The clinical characteristics and other laboratory data of the patients were compared.

Within the scope of the study, serum albumin, glucose, lactate dehydrogenase (LDH), urea, and creatinine were measured using the spectrophotometric method, and C-reactive protein (CRP) was measured using the immunoturbidimetric method in an auto analyzer. Complete blood count parameters were measured with the light emitting diode flow cell method. Prothrombin time (PT) was measured using the optical method, D-dimer by the latex agglutination test. For sCD163, the sera were stored at -80 °C until the working day. The serum sCD163 level was measured using the sandwich ELISA method (Elabsience, Bioassay Technology Laboratory, Shangai, China). In the precision study conducted by the manufacturer, the CV% of the kits within and between studies was given as <10%. Our study was approved by Sakarya University Non-Interventional Clinical Research Ethics Committee on 04/09/2020 with the decision number 71522473/050.01.04/462.

Statistical Analysis

Data analyses were performed using SPSS version 20 for Windows software (SPSS Inc. Chicago, IL, USA). The suitability of the variables to normal distribution was examined using Kolmogorov-Smirnov. Normally distributed data were compared with one away. Abnormally distributed data were evaluated with the Mann-Whitney U test. Categorical associations were assessed using the χ^2 test. Receiver operating curve (ROC) analysis was used to calculate for sCD163 the required cut-off values to distinguish survivor and non-survivor patients by calculating the area under the curve (AUC) of the ROC curves. The predictive value of the CD163 was determined by logistic regression analysis. Statistical significance was defined as $p \leq 0.05$.

RESULTS

Of the 79 cases included in the study, 37 (46.8%) were female. There was no significant difference in gender between the groups (p=0.407). The total number of survivors was 54 (68.4%), and the total number of non-survivors was 25 (31.6%). The mean age was 70.4±12 years in the non-survivors and 64.2±14 years in the survivors (p=0.079). Looking at the symptoms at the time of admission to the hospital, while 26 (48%) of the patients who survived had fever, only 6 (25%) of the patients with non-survivors had fever exceeding 38 °C (p=0.017). Twenty (37%) survivors and 18 (72%) of non-survivors had shortness of breath (p=0.004). Thirty (55%) of survivors and 10 (40%) of non-survivors had coughs (p=0.198). Twenty-two (22%) survivors and 5 (20%) of

non-survivors had fatigue (p=0.823). Eleven (20%) survivors and 2 (0.07%) of non-survivors had myalgia-arthralgia (p=0.310). Two (3.7%) survivors and 3 (12%) of non-survivors had throat ache (p=0.159).

Comorbidities such as hypertension and cerebrovascular disease were compared in terms of mortality and were found statistically significant (p=0.020, p=0.005, respectively) (Table 1).

sCD163, PT, and lactate was higher in the non-survivors than in the survivors (p=0.023, p=0.015, p=0.018, respectively). Compared to survivors d-dimer (p=0.029), ferritin (p=0.002), LDH (p<0.001), erythrocyte sedimentation rate (p=0.003), CRP (p=0.001), neutrophil count (p=0.001) and neutrophil to lymphocyte ratio (p=0.001) were found to be significantly higher in the non-survivors and the lymphocyte count was found to be significantly lower (p=0.001). The sCD163 levels were significantly higher in the non-survivors than

Table 1. Clinical, demographic and laboratory characteristics of patients with COVID-19

Characteristics	Survivor (n=54)	Non-survivor (n=25)	p-value
Age, years	64.2±14	70.4±12	0.079
Men	27 (50%)	15 (60%)	0.407
Women	27 (50%)	10 (40)	0.407
Hypertension	15 (28%)	11 (46%)	0.020
Diabetes mellitus	24 (48%)	13 (52%)	0.531
COLD	2 (3.7%)	0 (0%)	0.330
Asthma	3 (5.5%)	3 (12%)	0.315
CAD	7 (12.9%)	4 (16%)	0.717
Malignity	1 (1.85%)	3 (12.5%)	0.056
CVD	3 (5.5%)	7 (29%)	0.005
CRP (mg/L)	39 (13-109)	122 (55-168)	0.001
Sedimentation (mm/h)	41±20	59±19	0.003
Procalcitonin (ng/mL)	2.3±1.4	4.7±2	0.548
WBC (K/uL)	6355 (4915-8160)	9630 (6190-12000)	0.747
Neutrophil K/uL	4887±2400	7300±3312	0.001
Lymphocyte K/uL	1150 (857-1407)	639 (501-1018)	0.001
NLR	6.6±3.1	10.9±5.2	0.001
Hemoglobin (g/dL)	12.0±1.5	12.2±1.9	0.747
D-dimer (Ug/FEu)	564 (260-1310)	1210 (792-2120)	0.029
Ferritin (ug/L)	138 (67-387)	731 (296-1900)	0.002
Glucose (mg/dL)	139±66	157±57	0.056
Urea (mg/dL)	45 (29-56)	69 (38-85)	0.026
Creatinine (mg/dL)	1.0 (0.6-0.9)	1.3 (0.7-1.0)	0.500
Prothrombin time (sn)	12.7±2.8	14±1.9	0.015
INR	1.1±0.2	1.2±0.1	0.038
LDH (U/L)	345±150	495±173	0.001
Lactate (mmol/L)	1.65±0.5	2.02±0.7	0.018
CD163 (ng/mL)	2.81±0.8	3.47±1.7	0.023

Data are presented as mean (SD), for continuous variables with normal.

Distribution, median and 25th and 75th percentiles (P25-P75) for variables with non-normal distribution.

COLD: Chronic obstructive lung disease, CAD: Coronary artery disease, CVD: Cerebrovascular disease, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio; INR: International normalized ratio, WBC: White blood cells, LDH: Lactate dehydrogenase, COVID-19: Coronavirus disease-2019, SD: Standard deviation

in the survivors (3.47±1.7 vs. 2.81±0.8, p=0.023) (Table 1). Serum sCD163 levels of survivor and non-survivor COVID-19 patients are shown in Figure 1. The ROC curve analyzed the effect of sCD163 on mortality in hospitalized COVID-19 patients. The optimum cutoff value of serum sCD163 by ROC analysis was 2.92 ng/mL, resulting in 74% sensitivity and 52% specificity for predicting mortality (AUC: 0.620, p=0.048) (Figure 2). We built a logistic regression model for survival as a dependent variable, and CD163≥2.92, PT, and lactate as independent predictors. In the logistic regression, the mortality risk was found to be 4.3 times higher in CD163≥2.92 (p=0.014). The results of the logistic regression analysis are summarized in Table 2.

DISCUSSION

This study showed that the sCD163, PT, and lactate levels were significantly higher in non-survivors than in survivors. In previous studies, non-survivor patients with HIV (17), hepatitis B virus (18), and sepsis (19) had higher sCD163 levels, compared to survivors. Elevated plasma sCD163 levels are an independent predictor of death in HIV-positive adults (20) and hepatitis B infection (18). An increased sCD163 plasma concentration has been observed in diseases related to macrophage activity, including acute and chronic inflammations (9). CD163 staining in infiltrating macrophages was more evident in COVID-19 patients (21). Since sCD163 concentrations in viral infections are associated with mortality, it was thought that it may also be associated with COVID-19, which is a novel viral infection. Gómez-Rial et al. (21) found no difference between sCD163 levels in ICU and non-ICU patients, but showed that it was significantly higher in COVID-19 patients than in the healthy control group. Bowman et al. (22) found no difference in sCD163 levels when COVID-19 patients were categorized as mild, moderate, and critical, but a significant increase in sCD163 was shown in those who died. Our study showed that sCD163 levels were significantly higher in patients who died of COVID-19 than in survivors. There was a significant relationship between the admission sCD163 level and mortality. Our findings suggest that the sCD163 level, combined with patient features, can be used to identify individuals with poor prognoses and death.

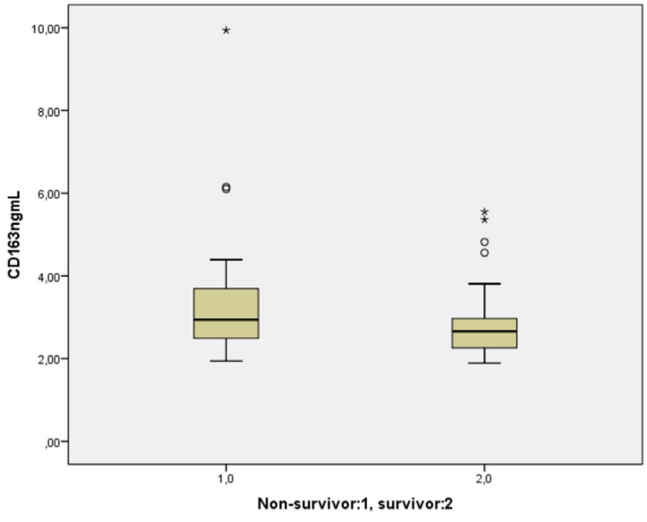

Figure 1. Serum sCD163 levels of survivor and non-survivor (p=0.023)
sCD163: Soluble CD163

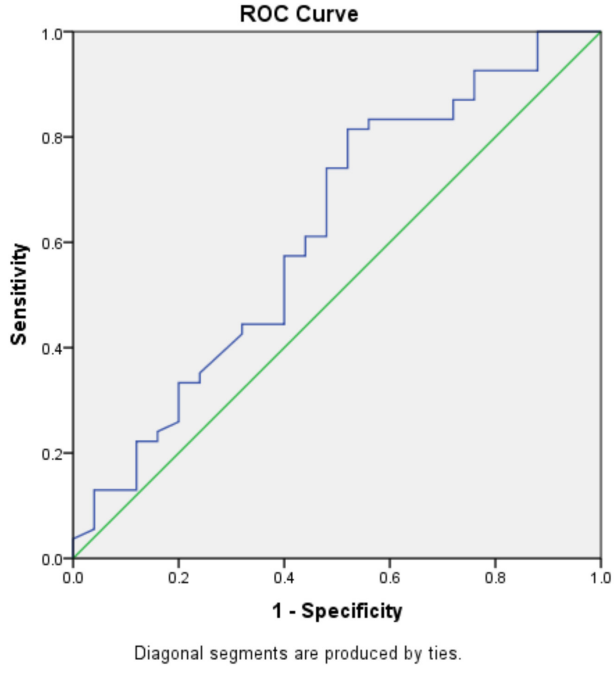

Figure 2. Receiver operating characteristic curve for CD163 ratio in patients with survivor or non-survivor COVID-19
ROC: Receiver operating characteristic, COVID-19: Coronavirus disease-2019

Table 2. Binary logistic regression analysis results of the parameters for survival

Parameters	B	SE	Wald	Odds ratio	p-value
CD163≥2.92	1.455	0.592	6.032	4.3	0.014
Prothrombin time	-0.664	-0.305	5.313	0.737	0.021
Lactate	-1.101	0.469	5.502	0.333	0.019

B: Standardized regression coefficients, SE: Standard error

Previous reports have shown that COVID-19 cases could be severe and fatal in individuals with comorbidities (3). In a multi-center cohort study conducted in China, diabetes mellitus and coronary artery disease were shown as the most common causes of comorbidity, respectively, after hypertension (23). In our study, diabetes mellitus, hypertension, cerebrovascular disease, and coronary artery disease was common in patients hospitalized for COVID-19 with a mortal course. Statistical significance with mortality was with hypertension and cerebrovascular disease. It was reported that elevated d-dimer levels, LDH, PT, and lymphopenia were commonly seen in severe COVID-19 (23). Our study showed that d-dimer, PT, LDH, and CRP were significantly higher in non-survivors than in survivors. The results were similar to those of the previous studies.

In one study, the mortality rate in hospitalized COVID-19 patients was 23.8% (24). According to the results of our research, the case fatality rate was 32%. 68% of the patients who died were older than 65 years. Although many factors affecting mortality have been elucidated, many unknowns are related to this disease.

COVID-19 is a novel disease, and it has been found in the literature that many pro-inflammatory cytokines and other acute phase reactant levels correlate with a poor prognosis (16). However, there are no specific biomarkers showing the prognosis of COVID-19 and their relationship with mortality. CD163 is a biomarker of inflammatory diseases. In this research, sCD163, PT, and lactate were associated with mortality in COVID-19 patients. In the logistic regression, when sCD163 was ≥2.92, the mortality risk was 4.3 times higher.

Our study has some limitations, including a single-center cohort study, the small sample size, a retrospective design, and the lack of anthropometric data due to the urgency of epidemics.

CONCLUSION

Serum sCD163 is a valuable biomarker indicating the prognosis of COVID-19 and is an independent predictor of mortality. Further studies may be useful in clarifying the role of serum sCD163 in COVID-19 severity.

ETHICS

Ethics Committee Approval: Our study was approved by Sakarya University Non-Interventional Clinical Research Ethics Committee on 04/09/2020 with the decision number 71522473/050.01.04/462.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.N., T.K., S.Y., D.Ç., K.S., C.K., E.Ç., C.B., Concept: S.Y., Design: S.Y., C.K., Data Collection or Processing: D.Ç., K.S., C.K., E.Ç., Analysis or Interpretation: A.N., T.K., E.Ç., C.B., Literature Search: A.N., S.Y., C.B., Writing: A.N., T.K.

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

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

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
2. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen MY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. J Microbiol Immunol Infect 2020;53:404-12.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
4. Madsen M, Møller HJ, Nielsen MJ, Jacobsen C, Graversen JH, van den Berg T,et al. Molecular characterization of the haptoglobin. hemoglobin receptor CD163. Ligand binding properties of the scavenger receptor cysteine-rich domain region. J Biol Chem 2004;279:51561-7.
5. Møller HJ, Nielsen MJ, Maniecki MB, Madsen M, Moestrup SK. Soluble macrophage-derived CD163: a homogenous ectodomain protein with a dissociable haptoglobin-hemoglobin binding. Immunobiology 2010;215:406-12.
6. Sulahian TH, Högger P, Wahner AE, Wardwell K, Goulding NJ, Sorg C, et al. Human monocytes express CD163, which is upregulated by IL-10 and identical to p155. Cytokine 2000;12:1312-21.
7. Bover LC, Cardó-Vila M, Kuniyasu A, Sun J, Rangel R, Takeya M, et al. A previously unrecognized protein-protein interaction between TWEAK and CD163: potential biological implications. J Immunol 2007;178:8183-94.
8. Van Gorp H, Van Breedam W, Delputte PL, Nauwynck HJ. Sialoadhesin and CD163 join forces during entry of the porcine reproductive and respiratory syndrome virus. J Gen Virol 2008;89:2943-53.
9. Møller HJ. Soluble CD163. Scand J Clin Lab Invest 2012;72:1-13.
10. Bleesing J, Prada A, Siegel DM, Villanueva J, Olson J, Ilowite NT, et al. The diagnostic significance of soluble CD163 and soluble interleukin-2 receptor alpha-chain in macrophage activation syndrome and untreated new-onset systemic juvenile idiopathic arthritis. Arthritis Rheum 2007;56:965-71.
11. Baeten D, Møller HJ, Delanghe J, Veys EM, Moestrup SK, De Keyser F. Association of CD163+ macrophages and local production of soluble CD163 with decreased lymphocyte activation in spondylarthropathy synovitis. Arthritis Rheum 2004;50:1611-23.
12. Bronkhorst IH, Ly LV, Jordanova ES, Vrolijk J, Versluis M, Luyten GP, et al. Detection of M2-macrophages in uveal melanoma and relation with survival. Invest Ophthalmol Vis Sci 2011;52:643-50.
13. Kazankov K, Barrera F, Møller HJ, Bibby BM, Vilstrup H, George J, et al. Soluble CD163, a macrophage activation marker, is

independently associated with fibrosis in patients with chronic viral hepatitis B and C. Hepatology 2014;60:521-30.

14. Møller HJ, Moestrup SK, Weis N, Wejse C, Nielsen H, Pedersen SS, et al. Macrophage serum markers in pneumococcal bacteremia: Prediction of survival by soluble CD163. Crit Care Med 2006;34:2561-6.
15. Burdo TH, Lo J, Abbara S, Wei J, DeLelys ME, Preffer F, et al. Soluble CD163, a novel marker of activated macrophages, is elevated and associated with noncalcified coronary plaque in HIV-infected patients. J Infect Dis 2011;204:1227-36.
16. Nalbant A, Kaya T, Varim C, Yaylaci S, Tamer A, Cinemre H. Can the neutrophil/lymphocyte ratio (NLR) have a role in the diagnosis of coronavirus 2019 disease (COVID-19)? Rev Assoc Med Bras (1992) 2020;66:746-51.
17. Generoso M, Álvarez P, Kravietz A, Mwamzuka M, Marshed F, Ahmed A, et al. High soluble CD163 levels correlate with disease progression and inflammation in Kenyan children with perinatal HIV-infection. AIDS 2020;34:33-8.
18. Ye H, Wang LY, Zhao J, Wang K. Increased CD163 expression is associated with acute-on-chronic hepatitis B liver failure. World J Gastroenterol 2013;19:2818-25.
19. Kjærgaard AG, Rødgaard-Hansen S, Dige A, Krog J, Møller HJ, Tønnesen E. Monocyte expression and soluble levels of the haemoglobin receptor (CD163/sCD163) and the mannose receptor (MR/sMR) in septic and critically ill non-septic ICU patients. PLoS One 2014;9:e92331.
20. Knudsen TB, Ertner G, Petersen J, Møller HJ, Moestrup SK, Eugen-Olsen J, et al. Plasma Soluble CD163 Level Independently Predicts All-Cause Mortality in HIV-1-Infected Individuals. J Infect Dis 2016;214:1198-204.
21. Gómez-Rial J, Currás-Tuala MJ, Rivero-Calle I, Gómez-Carballa A, Cebey-López M, Rodríguez-Tenreiro C, et al. Increased Serum Levels of sCD14 and sCD163 Indicate a Preponderant Role for Monocytes in COVID-19 Immunopathology. Front Immunol 2020;11:560381.
22. Bowman ER, Cameron CMA, Avery A, Gabriel J, Kettelhut A, Hecker M, et al. Levels of Soluble CD14 and Tumor Necrosis Factor Receptors 1 and 2 May Be Predictive of Death in Severe Coronavirus Disease 2019. J Infect Dis 2021;223:805-10.
23. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
24. Fadel FA, Al-Jaghbeer M, Kumar S, Griffiths L, Wang X, Han X, et al. Clinical characteristics and outcomes of critically Ill patients with COVID-19 in Northeast Ohio: low mortality and length of stay. Acute Crit Care 2020;35:242-8.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:303-309
DOI: 10.4274/BMJ.galenos.2022.2022.4-15

Research

Can Temporal Muscle Thickness Be a New Prognostic Factor for *De Novo* Glioblastoma?

Temporal Kas Kalınlığı Yeni Tanı Glioblastoma için Prognostik Faktör Olabilir mi?

Elif Eda Özer[1], Meltem Kırlı Bölükbaş[1], Mustafa Orhan Nalbant[2], Gülşen Pınar Soydemir[1], Metin Figen[1], Esengül Koçak Uzel[1]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Radiology, İstanbul, Turkey

ABSTRACT

Objective: Glioblastoma multiforme (GBM) is the most aggressive and commonly seen primary malignant brain tumor in adults. In addition to clinical, molecular and histopathological prognostic factors, sarcopenia, defined as low skeletal muscle mass, has become one of the important parameters. The relationship between skeletal muscle mass and temporal muscle thickness (TMT) has been demonstrated. We evaluated the prognostic value of TMT in patients with newly diagnosed GBM.

Methods: A total of 66 GBM patients were included in this retrospective study. Left and right TMT's from pre-operative magnetic resonance images were measured separately by an experienced radiologist, and the mean TMT value for each patient was calculated. The survival times and rates were examined with the Kaplan-Meier method. Overall survival (OS) was calculated from the day of diagnosis. The correlation coefficients and their significance were calculated using the Spearman test.

Results: The median right TMT was 4.4 (1.7-9.5) mm, the left TMT was 4.1 (1.5-9.6) mm. The median TMT was 4.38 (1.66-9.45) mm. Spearman correlation test revealed a slight correlation between the mean TMT value and the age at the diagnosis (p=0.044). Spearman correlation test for gender also showed a slight correlation between the mean TMT value and gender (p=0.024). In the multivariate analysis using the Cox regression model showed that increased TMT was a positive prognostic marker for OS in GBM patients (p=0.030).

Conclusion: TMT greater than 4.38 mm was found to be an independent prognostic factor in *de novo* glioblastoma. However, studies with larger series are needed to generalize this result to the Turkish population.

Keywords: Glioblastoma, sarcopenia, prognosis, temporal muscle

ÖZ

Amaç: Glioblastoma multiforme (GBM), yetişkinlerde görülen en agresif primer malign beyin tümörüdür. Klinik, moleküler ve histopatolojik faktörlerin yanı sıra düşük iskelet kası kütlesi olarak tanımlanan sarkopeni önemli prognostik faktörlerden biri haline gelmiştir. İskelet kası kütlesi ile temporal kas kalınlığı (TMT) arasındaki ilişki ortaya konmuştur. Çalışmamızda yeni tanı konmuş GBM'li hastalarda TMT'nin prognostik değerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya GBM tanısı olan 66 hasta dahil edildi. Ameliyat öncesi manyetik rezonans görüntülerinden sol ve sağ TMT'ler deneyimli bir radyolog tarafından ayrı ayrı ölçüldü ve her hasta için ortalama TMT değeri hesaplandı. Yaşam süreleri ve oranları Kaplan-Meier yöntemi ile incelendi. Genel sağkalım (OS) tanı gününden itibaren hesaplandı. Korelasyon katsayıları ve anlamlılıkları Spearman testi kullanılarak hesaplandı.

Bulgular: Medyan sağ TMT 4,4 (1,7-9,5) mm, sol TMT 4,1 (1,5-9,6) mm idi. Medyan TMT 4,38 (1,66-9,45) mm idi. Spearman korelasyon testi, ortalama TMT değeri ile tanı yaşı arasında hafif bir korelasyon olduğunu ortaya koydu (r=-0,248, p=0,044). Cinsiyete göre Spearman korelasyon testi de ortalama TMT değeri ile cinsiyet arasında hafif bir korelasyon gösterdi (r=-0,277, p=0,024). Cox regresyon analizi kullanılarak yapılan multivaryant analizde TMT'nin toplam OS için pozitif prognostik bir marker olduğu gösterildi (p=0,030).

Address for Correspondence: Esengül Koçak Uzel, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
Phone: +90 536 417 39 25 E-mail: dresengulkocakuzel@gmail.com ORCID ID: orcid.org/0000-0001-6953-6805

Cite as: Özer EE, Kırlı Bölükbaş M, Nalbant MO, Soydemir GP, Figen M, Koçak Uzel E. Can Temporal Muscle Thickness Be a New Prognostic Factor for *De Novo* Glioblastoma?. Med J Bakirkoy 2022;18:303-309

Received: 14.04.2022
Accepted: 24.06.2022

Sonuç: TMT'nin 4,38 mm'den büyük olmasının *de novo* glioblastomda bağımsız bir prognostik faktör olduğu bulundu. Ancak bu sonucun Türk toplumuna genellenmesi için daha geniş serili çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Glioblastoma, sarkopeni, prognoz, temporal kas

INTRODUCTION

Glioblastoma multiforme (GBM) is the most aggressive and commonly seen primary malignant brain tumor in adults (1). GBM accounts for 52% of all primary brain tumors and 60%-70% of gliomas (2). Glioblastomas are more common in men than in women. The median age of patients at the time of diagnosis is 64 years (3). Median survival in GBM is usually 14,6 months after diagnosis, and long-term survival is rare (4). Surgical resection within safe limits followed by adjuvant radiotherapy (RT) and chemotherapy is the standard treatment approach for GBM. Concurrent and adjuvant temozolomide (TMZ) improves the median 2- and five-year survival of patients with glioblastoma (4). Prognostic factors are age at diagnosis, performance status (PS), the extent of resection, duration of symptoms, O-6-methylguanine-DNA methyltransferase (MGMT) status, and neurological functional/mental status (3).

In addition to all these clinical, molecular, and histopathological data, sarcopenia, defined as low skeletal muscle mass, has become one of the important parameters to be considered, particularly in cancer patients recently. However, objective measurement of sarcopenia is required. It is a parameter that indicates the prognosis and survival in various types of extracranial cancers (5-8). Previously, skeletal muscle mass measurement was performed on abdominal computed tomography (CT) at the third lumbar vertebra level (L3) (5,9,10). However, it was impossible to measure skeletal muscle mass, whereas routine abdominal CT scans are not performed, such as in head and neck or nervous system cancers. Therefore, muscle mass measurement from the third cervical vertebra (C3) level was presented as an alternative to the L3 vertebra level in head and neck cancer studies (11,12). Studies supporting sarcopenia regarding the prediction of clinical outcomes of brain tumor patients in the literature are limited compared with other cancers. After demonstrating a relationship between skeletal muscle mass and temporal muscle thickness (TMT), (13) studies were published reporting TMT as an independent prognostic parameters in patients with newly diagnosed brain metastases (14,15). Subsequently, based on these studies, researches have conducted that report TMT's prognostic value in patients with recurrent GBM. There have also been studies on its use as a marker (15-18).

Our study aimed to evaluate the prognostic value of TMT for overall survival (OS) rate and to investigate the importance of TMT as a marker of muscle loss in patients with newly diagnosed GBM. Also, it is to retrospectively analyze the prognostic relationship of TMT with known factors such as age, resection type, and PS of GBM patients.

METHODS

Patients Selection and Treatment

The study included 66 patients with GBM diagnosis and pre-operative magnetic resonance (MR) images who received simultaneous/adjuvant TMZ and postoperative RT. Additionally, patients' age, gender, The European Cooperative Oncology Group (ECOG) performance score, tumor diameter, Ki-67 index, tumor location, mean TMT, date of diagnosis, treatment details, last follow-up, and death information were recorded. Approval was obtained from the Clinical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital for our study (decision no: 2021-11-14, date: 07.06.2021).

According to the planning target volume (PTV), all patients received a median dose of 60 Gy (59.4-64 Gy) of RT once a day, 2.0 Gy per fraction, according to the PTV, using the volumetric arc therapy treatment method with a 6 million volt linear accelerator. TMZ chemotherapy was planned for all patients. Concurrent 75 mg/m^2/day TMZ RT was initiated from the first day of RT and continued throughout RT. Adjuvant TMZ was started four weeks after the end of RT. While the adjuvant TMZ dose was 150 mg/m^2 for the first cycle, it was increased to 200 mg/m^2 per day for five days every 28 days after the second cycle in patients without hematological toxicity.

Before surgery, all patients underwent 1.5 Tesla (Siemens Amira) contrast-enhanced MR imaging. TMT at diagnosis of GBM was measured on T1-weighted contrast-enhanced axial brain MR images, at the level of the orbital roof perpendicularly to the long axis of the temporal muscle on an axial plane, which was oriented parallel to the anterior-posterior commissure line. Left and right TMT's were measured separately by an experienced radiologist, and the mean TMT value for each patient was calculated. The orbital roof and Sylvian fissure are used as anatomical landmarks for more accurate assessments. The radiologist was blinded to the patients' results, clinical features, and survival data. Patients with post-therapeutic changes that affected TMT were excluded from further evaluation. The measurements also included the diameter of the mass before surgery and the cavity diameter in post-op patients (Figure 1).

Survival status and/or death dates were obtained by searching each patient' file data. OS was defined as the number of days between the initial surgery and death. Patients who were confirmed as alive on December 31, 2021 were entered into the database.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) v.22 (SPSS, Chicago, IL, USA) was used for the statistical analysis. The mean TMT was calculated by taking the arithmetic mean of the right and left TMTs. Based on the median value of the mean TMT, the patients were divided into thin and thick temporal muscle groups. The descriptive and frequency statistics were calculated, and the chi-square test was conducted to evaluate the differences in categorical variables. The survival times and rates were examined with the Kaplan-Meier method. OS was calculated from the day of diagnosis. The correlation coefficients and their significance were calculated using the Spearman test. The factors affecting the OS were evaluated using Log-rank and Cox regression tests. A p-value <0.05 is considered statistically significant.

RESULTS

Sixty-six patients were included in the study, and their descriptive characteristics are listed in Table 1. The median age of the patients was 57 (24-83) years. Twenty-eight patients were female, and 38 patients were male. According to PS, 15 patients (54.9%) had an ECOG score of 0-1, while 52 patients had an ECOG score of ≥2. The most common tumor localizations were temporal lobe (23/66, 34.8%), frontal lobe (21/66, 31.8%), and parietal lobe (14/66, 18.2%), and less frequently other regions. Gross total resection was performed in approximately half of the patients (n=32, 48.5%). There were 19 (28.8%) patients who had an isocitrate dehydrogenase (IDH)1 mutation. The median PTV 60 volume was 265 (126.5-829.2) cc. The median right TMT was 4.4 (1.7-9.5) mm, the left TMT was 4.1 (1.5-9.6) mm. The median TMT was 4.38 (1.66-9.45) mm. Concomitant TMZ was applied to all patients. With adjuvant therapy, 50% of the patients received six cycles or less of TMZ, while the other half received more than six cycles of TMZ. The mean follow-up period was 14.0 months (1-123 months). Up to the last follow-up visit, 36 (54.5 %) patients died, and the median OS was 11.3 (1.2-49.4) months.

The patients were divided into two groups according to the median TMT (4.38 mm). The characteristics of the two groups according to the median TMT are shown in Table 2.

The strength of the association between the two variables was calculated using the Spearman correlation coefficient. Spearman correlation test revealed a slight correlation between the mean TMT value and the age at the diagnosis (r =-0.248, p=0.044). It was shown that TMT thickness decreased with increasing age. A slight correlation was not reflected in the log-rank test at the level of statistical significance (p=0.581). Spearman correlation test for gender also showed a slight correlation between the mean TMT value and gender (r =-0.277, p=0.024). The mean TMT in men [median 4.5 mm (2.3-9.4 mm)] was higher than in women [median 3.9 mm (1.6-8.8 mm)]. However, thicker TMT in men did not have a positive effect on survival (p=0.53).

A log-rank test was used to identify the factors on OS. The gender, age, tumor or cavity volume, PTV 60 volume, ECOG-PS, operation type, IDH 1 mutation, Ki-67 index, number of adjuvant TMZ cycles, and TMT were examined for univariate analysis. ECOG-PS ≤2 (p=0.036), IDH mutant type (p=0.05), >6 cycles of adjuvant TMZ treatment (p=0.006), and younger age (p=0.002) were found significant factors for OS.

In the multivariate survival analysis using a Cox regression model showed that ECOG ≤2 [hazard ratio (HR) 8.292; 95% confidence interval (CI) 1.684-40.834; p=0.009], gross total resection (HR 3.906; 95% CI 1.087-14.033; p=0.037),

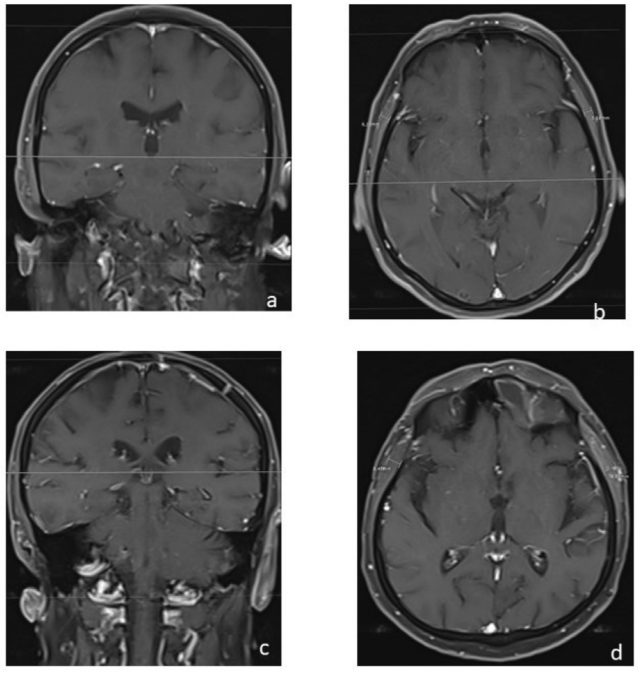

Figure 1. Representative TMT assessment on contrast-enhanced cranial T1-weighted MR images. Coronal (a), axial (b) images of a female patient (mean TMT =5.68 mm) and coronal (c) and axial (d) views of a male patient (mean TMT =8.56 mm) TMT was measured at the level of the orbital roof perpendicularly to the long axis of the temporal muscle on an axial plane, which was oriented parallel to the anterior-posterior commissure line

TMT: Temporal muscle thickness, MR: Magnetic resonance

Table 1. The descriptive analysis of the entire study group

Gender	
Female	28 (42.4%)
Male	38 (57.6%)
Age (min-max)	57 (24-83)
ECOG performance score	
<2	52 (78.8%)
≥2	14 (21.2%)
The side of the tumor	
Right	38 (57.6%)
Left	28 (42.4%)
The location of the tumor	
Frontal	21 (31.8%)
Temporal	23 (34.8%)
Parietal	12 (18.2%)
Occipital	4 (6.1%)
Temporoparietal	2 (3.0%)
Parietoccipital	4 (6.1%)
The form of the surgery	
Total resection	32 (48.5%)
Subtotal resection	19 (28.8%)
Biopsy	15 (22.7%)
IDH mutation	
Wild	47 (71.2%)
Mutant	19 (28.8%)
Ki-67	
≤20	40 (60.6%)
>20	26 (39.4%)
The diameter of the tumor (mm)	12.9 (1.0-65.0)
The diameter of the operation cavity (mm)	20.6 (2.0-68.0)
PTV 60 (cc)	265.0 (126.5-829.2)
The thickness of the right temporal muscle (mm)	4.4 (1.7-9.5)
The thickness of the left temporal muscle (mm)	4.1 (1.5-9.6)
The median of the mean temporal muscle thickness (mm)	4.38 (1.66-9.45)

Min: Minimum, Max: Maximum, ECOG: Eastern Cooperative Oncology Group, IDH: Isocitrate dehydrogenase, PTV: Planning target volume, *Chi-square test

presence of IDH mutation (HR 4.656; 95% CI 1.332-16.273; p=0.016) and, >6 courses of adjuvant TMZ (HR 0.005; 95% CI 0.000-0.0.061; p=0.000) were significantly associated with the OS time of GBM patients. Additionally, TMT was a prognostic marker for OS in GBM patients (HR 10.786; 95% CI 1.257-92.544; p=0.030) (Figure 2). There was no significant association between the survival of GBM patients and gender, age at diagnosis, tumor or cavity volume, PTV 60 volume, and Ki-67 index (p>0.05).

DISCUSSION

Sarcopenia is defined as the loss of skeletal muscle mass. It is used as an important and independent biomarker in cancer prognosis. Sarcopenia has recently started to be used in neuro-oncological patients. In the study of Ranganathan et al. (13) on trauma patients in 2014, TMT was reported as an ideal marker of sarcopenia. TMT measurement studies in neuro-oncological patients were frequently conducted for brain metastases (14). Leitner et al. (14) suggested the use of TMT for sarcopenia in brain metastases, stating that L3 and TMT were correlated with brain metastases. In current studies, studies on TMT are performed on patients with progressive and newly diagnosed GBM (16,18-22).

In our study, 66 patients with de-novo GBM were examined with pre-operative MR images. When the mean TMT was calculated, the mean TMT of our study group was found to be lower than all other groups (16,20-22). Many factors affect TMT, such as tumor type, trauma, surgery, infection, nutrition, and age (21,23,24). However, the fact that the mean TMT value determined in our study was consistent with the value in the study of Yesil Cinkir and Colakoglu Er (18), which

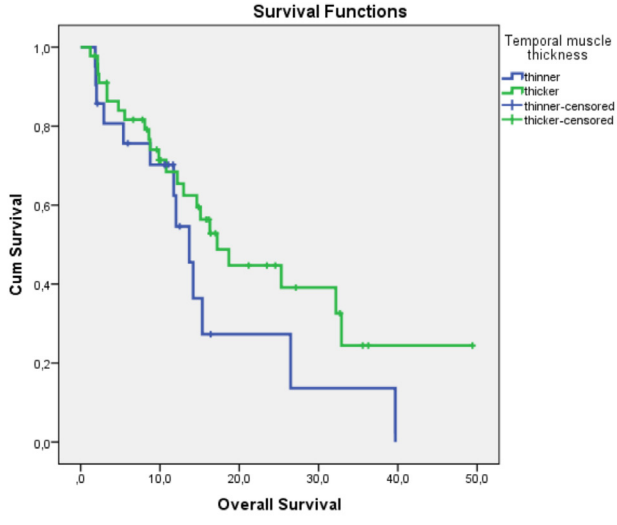

Figure 2. The effect of temporal muscle thickness on overall survival (p=0.03)

is also a Turkish study, showed that geographic and ethnic origin might also affect TMT. When the characteristics were examined, although the gender difference was not significant according to our study in contrast with other studies, TMT was higher in the male gender than in the female gender. However, this difference was not reflected in OS.

The median age of the patients included in the study was 57, which is consistent with the literature. The probability of developing sarcopenia increases with advancing age (8,25). In our study, we found a slight correlation between the TMT decrease and advancing age. In a report by The European Working Group on Sarcopenia in Older People, it was revealed that the cause of sarcopenia might be age-

Table 2. The descriptive analysis according to the temporal muscle thickness

	Thinner TM (n=33)	Thicker TM (n=33)	p*
	Median (min-max)	Median (min-max)	
Gender			0.046
Female	18 (54.4%)	10 (30.3%)	
Male	15 (45.5%)	23 (69.7%)	
Age (years)			0.218
<57 (median)	14 (42.4%)	19 (57.6%)	
≥57 (median)	19 (57.6%)	14 (42.4%)	
ECOG performance score			0.228
<2	24 (72.7%)	28 (84.8%)	
≥2	9 (27.3%)	5(15.2%)	
The side of the tumor			0.618
Right	18 (54.5%)	20 (60.6%)	
Left	15 (45.5%)	13 (39.4%)	
The form of the surgery			0.378
Total and subtotal resection	24 (72.7%)	27 (81.8%)	
Biopsy	9 (27.3%)	6 (18.2%)	
IDH mutation			0.786
Wild	24 (72.7%)	23 (69.7)	
Mutant	9 (27.3%)	10 (30.3)	
Ki-67 group			0.114
≤20	12 (50.0%)	12 (75.0%)	
>20	12 (50.0%)	4 (25.0%)	
The diameter of the tumor/operation cavity (mm)			0.453
35 mm and below	21 (63.6%)	18 (54.5%)	
Over 35 mm	12 (36.4%)	15 (44.5%)	
PTV 60 (cc)			0.026
265 and below	14 (42.4%)	23 (29.7%)	
265 and over	19 (57.6%)	10 (30.3%)	
Adjuvant temozolomide usage			0.460
≤6 cycles	15 (45.5%)	18 (54.5%)	
>6 cycles	18 (54.5%)	15 (45.5%)	

TM: Temporal muscle, Min: Minimum, Max: Maximum, ECOG: Eastern Cooperative Oncology Group, IDH: isocitrate dehydrogenase, PTV: Planning target volume, *Chi-square test

related primary sarcopenia, as well as decreased physical activity with a sedentary life, the patient's comorbidities (inflammatory, oncological, endocrinological) and secondary causes such as malabsorption and nutrition (25). The slight correlation detected between increasing age and decreasing TMT in our study was not reflected in the log-rank test at the level of statistical significance. Similarly, age was not found as a significant prognostic factor in the studies by Yesil Cinkir and Colakoglu Er (18) and An et al. (21). Huq et al.'s (20) study consisting of 381 patients with newly diagnosed and progressive GBM reported that TMT was associated with age, albumin, body mass index (BMI), and Karnofsky perfomance score (KPS). Albumin and BMI are directly related to nutrition and sarcopenia (26). However, because of the retrospective design of our study, patients' albumin and BMI levels were excluded from the analysis.

In the multivariate analysis of our study, ECOG ≤2, gross total resection (GTR), IDH mutation, TMZ more than six cycles, and thick TMT were found among the prognostic factors that positively affected OS. An et al. (21) reported low ECOG, GTR, and thick TMT, Liu et al. (22) reported thick TMT, age at diagnosis, and concomitant CRT, and Yesil Cinkir and Colakoglu Er (18) reported age and thick TMT to be good prognostic factors. Unlike these studies, which found a significant relationship between thick TMT and OS, Huq et al. (20) showed that TMT did not affect OS in newly diagnosed GBM but positively affected survival in progressive GBM. Muglia et al. (16) studied a small but homogeneous group of 51 patients diagnosed with methylated MGMT promoter, IDH1-2 wild-type glioblastoma, who underwent complete surgical resection followed by RT with concomitant and maintenance TMZ treatment. TMT of all patients was measured bilaterally from pre-operative MR images. The mean TMT was 8.43 mm. TMT was not associated with prognosis, age, or ECOG-PS. TMT has been argued to be an ineffective marker for predicting survival in GBM patients with newly diagnosed and untreated IDH1-2 wild-type, methylated-MGMT (16). However, the small number of patients and the fact that the patients are in the more aggressive group may be a reasons that suppress the effect of TMT.

Our study has some limitations. Initially, the patients included in the study caused a molecular and genetic heterogeneity pattern due to the retrospective design. Although our results were consistent with many studies in the literature, they differed from some studies examining a homogeneous patient group (16). Also, because of the retrospective study design, no additional research was conducted on other factors affecting TMT, such as patients' nutritional status and oral-dental health. Further studies with a larger sample size are needed to support our results and represent the Turkish population.

CONCLUSION

TMT greater than 4.38 mm was found to be an independent prognostic factor in de-novo glioblastoma. However, studies with larger series are needed to generalize this result to the Turkish population.

ETHICS

Ethics Committee Approval: Approval was obtained from the Clinical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital for our study (decision no: 2021-11-14, date: 07.06.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.E.Ö., M.O.N., E.K.U., Concept: E.E.Ö., M.K.B., G.P.S., E.K.U., Design: G.P.S., E.K.U., Data Collection or Processing: E.E.Ö., M.O.N., M.F., Analysis or Interpretation: M.K.B., E.K.U., Literature Search: E.E.Ö., M.O.N., M.F., E.K.U., Writing: E.E.Ö., G.P.S.

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

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

REFERENCES

1. Suzuki Y, Shirai K, Oka K, Mobaraki A, Yoshida Y, Noda SE, et al. Higher pAkt expression predicts a significant worse prognosis in glioblastomas. J Radiat Res 2010;51:343-8.
2. Baur M, Preusser M, Piribauer M, Elandt K, Hassler M, Hudec M, et al. Frequent MGMT (0(6)-methylguanine-DNA methyltransferase) hypermethylation in long-term survivors of glioblastoma: a single institution experience. Radiol Oncol 2010;44:113-20.
3. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst 1993;85:704-10.
4. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
5. Panje CM, Höng L, Hayoz S, Baracos VE, Herrmann E, Garcia Schüler H, et al. Skeletal muscle mass correlates with increased toxicity during neoadjuvant radiochemotherapy in locally advanced esophageal cancer: A SAKK 75/08 substudy. Radiat Oncol 2019;14:166.
6. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. Eur J Cancer 2016;57:58-67.
7. Huang X, Ma J, Li L, Zhu XD. Severe muscle loss during radical chemoradiotherapy for non-metastatic nasopharyngeal carcinoma predicts poor survival. Cancer Med 2019;8:6604-13.

8. Park SE, Hwang IG, Choi CH, Kang H, Kim BG, Park BK, et al. Sarcopenia is poor prognostic factor in older patients with locally advanced rectal cancer who received preoperative or postoperative chemoradiotherapy. Medicine (Baltimore) 2018;97:e13363.
9. Grossberg AJ, Chamchod S, Fuller CD, Mohamed AS, Heukelom J, Eichelberger H, et al. Association of Body Composition With Survival and Locoregional Control of Radiotherapy-Treated Head and Neck Squamous Cell Carcinoma. JAMA Oncol 2016;2:782-9.
10. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 2009;15:2920-6.
11. Swartz JE, Pothen AJ, Wegner I, Smid EJ, Swart KM, de Bree R, et al. Feasibility of using head and neck CT imaging to assess skeletal muscle mass in head and neck cancer patients. Oral Oncol 2016;62:28-33.
12. Zwart AT, van der Hoorn A, van Ooijen PMA, Steenbakkers RJHM, de Bock GH, Halmos GB. CT-measured skeletal muscle mass used to assess frailty in patients with head and neck cancer. J Cachexia Sarcopenia Muscle 2019;10:1060-9.
13. Ranganathan K, Terjimanian M, Lisiecki J, Rinkinen J, Mukkamala A, Brownley C, et al. Temporalis muscle morphomics: the psoas of the craniofacial skeleton. J Surg Res 2014;186:246-52.
14. Leitner J, Pelster S, Schöpf V, Berghoff AS, Woitek R, Asenbaum U, et al. High correlation of temporal muscle thickness with lumbar skeletal muscle cross-sectional area in patients with brain metastases. PLoS One 2018;13:e0207849.
15. Furtner J, Genbrugge E, Gorlia T, Bendszus M, Nowosielski M, Golfinopoulos V, et al. Temporal muscle thickness is an independent prognostic marker in patients with progressive glioblastoma: translational imaging analysis of the EORTC 26101 trial. Neuro Oncol 2019;21:1587-94.
16. Muglia R, Simonelli M, Pessina F, Morenghi E, Navarria P, Persico P, et al. Prognostic relevance of temporal muscle thickness as a marker of sarcopenia in patients with glioblastoma at diagnosis. Eur Radiol 2021;31:4079-86.
17. Zhang F, Wang Y, Xu W, Jiang H, Liu Q, Gao J, et al. Dosimetric Evaluation of Different Intensity-Modulated Radiotherapy Techniques for Breast Cancer After Conservative Surgery. Technol Cancer Res Treat 2015;14:515-23.
18. Yesil Cinkir H, Colakoglu Er H. Is temporal muscle thickness a survival predictor in newly diagnosed glioblastoma multiforme? Asia Pac J Clin Oncol 2020;16:e223-7.
19. Furtner J, Berghoff AS, Albtoush OM, Woitek R, Asenbaum U, Prayer D, et al. Survival prediction using temporal muscle thickness measurements on cranial magnetic resonance images in patients with newly diagnosed brain metastases. Eur Radiol 2017;27:3167-73.
20. Huq S, Khalafallah AM, Ruiz-Cardozo MA, Botros D, Oliveira LAP, Dux H, et al. A novel radiographic marker of sarcopenia with prognostic value in glioblastoma. Clin Neurol Neurosurg 2021;207:106782.
21. An G, Ahn S, Park JS, Jeun SS, Hong YK. Association between temporal muscle thickness and clinical outcomes in patients with newly diagnosed glioblastoma. J Cancer Res Clin Oncol 2021;147:901-9.
22. Liu F, Xing D, Zha Y, Wang L, Dong W, Li L, et al. Predictive Value of Temporal Muscle Thickness Measurements on Cranial Magnetic Resonance Images in the Prognosis of Patients With Primary Glioblastoma. Front Neurol 2020;11:523292.
23. Dallmann R, Weyermann P, Anklin C, Boroff M, Bray-French K, Cardel B, et al. The orally active melanocortin-4 receptor antagonist BL-6020/979: a promising candidate for the treatment of cancer cachexia. J Cachexia Sarcopenia Muscle 2011;2:163-74.
24. Dunne RF, Loh KP, Williams GR, Jatoi A, Mustian KM, Mohile SG. Cachexia and Sarcopenia in Older Adults with Cancer: A Comprehensive Review. Cancers (Basel) 2019;11:1861.
25. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.
26. Dasenbrock HH, Liu KX, Chavakula V, Devine CA, Gormley WB, Claus EB, et al. Body habitus, serum albumin, and the outcomes after craniotomy for tumor: a National Surgical Quality Improvement Program analysis. J Neurosurg 2017;126:677-89.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:310-315
DOI: 10.4274/BMJ.galenos.2022.2022.6-7

Research

Effect of the Adrenalectomy and Mineralocorticoid Receptor Antagonists on the Clinical and Biochemical Outcomes in Patients with Primary Aldosteronism: A Single-center Experience

Primer Hiperaldosteronizmli Hastalarda Adrenalektomi ve Mineralokortikoid Reseptör Antagonist Tedavinin Klinik ve Biyokimyasal Sonuçlara Etkisi: Tek Merkez Deneyimi

Seda Turgut, Hamide Pişkinpaşa

University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Endocrinology and Metabolism, İstanbul, Turkey

ABSTRACT

Objective: Primary hyperaldosteronism (PA) is a disorder in which non-suppressible hypersecretion of aldosterone from the adrenal gland. Treatment with either mineralocorticoid receptor antagonists (MRA) or unilateral adrenalectomy (ADX) of PA resolves hypokalemia, lowers blood pressure and ameliorates the parameters of impaired cardiac and renal function but may paradoxically result in a decline in estimated glomerular filtration rate (eGFR). This study compared the effects of ADX and MRA on clinical and biochemical outcomes in patients with PA.

Methods: Sixty-two patients with PA were recruited for this study. The patients were divided into two groups according to the PA treatment method. Group 1 (n=40) was defined as patients treated with MRA, and group 2 (n=22) was defined as patients who underwent ADX. Groups were compared in terms of creatinine, eGFR, potassium, sodium, plasma aldosterone concentration (PAC), plasma renin activity (PRA), aldosterone/renin ratio (ARR), presence of hypertension, and the percentage change in creatinine, eGFR, potassium, sodium. The correlation analysis between the percentage change in eGFR and the percent change of potassium with clinical and laboratory parameters was also performed.

Results: The mean age of the whole study group was 54.0±9.9 years. All patients had hypertension at baseline, and 11 patients (50%) had complete clinical success with hypertension without antihypertensive drugs after the treatment with ADX. Forthy-one patient had hypokalemia at baseline, and all of them resolved after the treatment with MRA or ADX. PAC, ARR, patients with hypokalemia, the percent change in eGFR and potassium were significantly higher in group 2 than in group 1 ($p<0.001$, $p=0.006$, $p=0.011$, $p=0.031$, and $p<0.001$; respectively). Significant positive correlations were observed between the percent change in eGFR and the percent change of potassium with PAC and ARR in the whole study group.

Conclusion: ADX could provide more benefit to renal function and resolve hypertension than the treatment of MRA. Aldosterone-induced glomerular hyperfiltration in PA resolves after both treatments and results in a more prominent decline in eGFR. Therefore, physicians should reevaluate the renal function after the treatments because pretreatment eGFR alone may not be a good predictor of renal function.

Keywords: Primary hyperaldosteronism, mineralocorticoid receptor antagonist, unilateral adrenalectomy, estimated glomerular filtration rate

ÖZ

Amaç: Primer hiperaldosteronizm (PA), adrenalden baskılanamayan aşırı aldosteron salgılanması ile karakterize bir hastalıktır. Uygun olmayan şekilde yüksek aldosteron üretimi, hipertansiyona, kardiyovasküler hasara, böbrek hasarı gelişimine ve hipokalemiye neden olmaktadır. PA'nın mineralokortikoid reseptör antagonistleri (MRA) veya tek taraflı adrenalektomi (ADX) ile tedavisi hipokalemiyi giderir, kan basıncını düşürür ve bozulmuş kardiyak ve renal fonksiyon parametrelerini iyileştirir, ancak paradoksal olarak tahmini glomerüler filtrasyon hızında (eGFR) bir düşüşe neden olabilir. PA ile ilgili güncel kılavuzlar, ADX'in MRA ile tıbbi tedaviye üstünlüğünü gösteren çalışmalardan dolayı tek taraflı aldosteron

Address for Correspondence: Seda Turgut, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Endocrinology and Metabolism, İstanbul, Turkey
Phone: +90 212 414 71 71 E-mail: seda.dr@gmail.com ORCID ID: orcid.org/0000-0003-1700-0181

Cite as: Turgut S, Pişkinpaşa H. Effect of the Adrenalectomy and Mineralocorticoid Receptor Antagonists on the Clinical and Biochemical Outcomes in Patients with Primary Aldosteronism: A Single-center Experience. Med J Bakirkoy 2022;18:310-315

Received: 10.06.2022
Accepted: 28.06.2022

salgılayan adenomlar için ADX'i önermektedir. Bu çalışmada, PA'lı hastalarda ADX ve MRA'nın klinik ve biyokimyasal sonuçlar üzerindeki etkilerinin karşılaştırılması amaçlandı.

Gereç ve Yöntem: 2015-2021 yılları arasında PA tanısı alan hastaların tıbbi kayıtları incelendi. Altmış iki hastaya PA teşhisi konuldu ve belgelenmiş uzun vadeli takip verileri olan hastalar çalışmaya dahil edildi. Hastalar PA tedavi yöntemine göre iki gruba ayrıldı. Grup 1 (n=40) MRA ile tedavi edilen hastalar, grup 2 (n=22) ADX uygulanan hastalar olarak tanımlandı. Gruplar arasında kreatinin, eGFR, potasyum, sodyum, plazma aldosteron konsantrasyonu (PAC), plazma renin aktivitesi (PRA), aldosteron/renin oranı (ARR), hipertansiyon varlığı ve kreatinin, EGFR, sodyum, potasyum değişim yüzdeleri açısından karşılaştırıldı. eGFR değişim yüzdesi ve potasyumun değişim yüzdesi ile klinik ve laboratuvar parametreleri arasında korelasyon analizi de yapıldı.

Bulgular: Tüm çalışma grubunun yaş ortalaması 54,0±9,9 yıl idi. Tüm çalışma grubunda ortalama PAC ve PRA seviyeleri sırasıyla 40,6±36,6 ng/dL ve 0,34±0,22 ng/mL/saat olarak saptandı. Tüm hastalarda başlangıçta hipertansiyon vardı ve 11 hastada (%50) ADX ile tedaviden sonra antihipertansif ilaçlar olmaksızın hipertansiyonda tam klinik başarı elde edildi. Kırk bir hastada başlangıçta hipokalemi vardı ve hepsi MRA veya ADX ile tedaviden sonra düzeldi. PAC, ARR ve hipokalemisi olan hastalar grup 2'de grup 1'e göre anlamlı olarak daha yüksekti (sırasıyla p<0,001, p=0,006 ve p=0,011). Grup 2'deki eGFR, potasyum değişim yüzdesi grup 1'den anlamlı olarak daha büyüktü (sırasıyla p=0,031 ve p<0,001). Tüm çalışma grubunda eGFR değişim yüzdesi ve potasyum değişim yüzdesi ile PAC ve ARR arasında anlamlı pozitif korelasyonlar gözlendi.

Sonuç: ADX böbrek fonksiyonuna MRA tedavisinden daha fazla fayda sağlayabilir ve hipertansiyonu MRA tedavisinden daha fazla düzeltebilir. Ancak MRA tedavisi de özellikle ADX için aday olmayan hastalar için etkin bir tedavi seçeneği olarak düşünülebilir. PA'da aldosteron kaynaklı glomerüler hiperfiltrasyon, tedaviden sonra düzelir ve bu hastalarda daha belirgin bir eGFR düşüşü gözlenir. Bu nedenle, tedavi öncesi eGFR tek başına böbrek fonksiyonunun iyi bir göstergesi olmayabileceğinden, klinisyenler tedaviden sonra böbrek fonksiyonunu yeniden değerlendirmelidir.

Anahtar Kelimeler: Primer hiperaldosteronizm, mineralokortikoid reseptör antagonisti, unilateral adrenalektomi, tahmini glomerüler filtrasyon hızı

INTRODUCTION

Primary hyperaldosteronism (PA) is a group of disorders in which non-suppressible hypersecretion of aldosterone from the adrenal gland (1-3). Inappropriately elevated production of aldosterone in PA causes hypertension, cardiovascular damage, hypokalemia, and suppression of plasma renin. The most common causes of PA are bilateral idiopathic hyperaldosteronism (60 to 70 percent) and unilateral aldosterone-secreting adenomas (30 to 40 percent) (1,3). PA is estimated to be responsible for 5 to 13 percent of hypertension in the population and is the most common cause of secondary hypertension (1,3,4). Non-suppressing hypersecretion of aldosterone is currently increasingly diagnosed in patients with hypertension but is still an underdiagnosed cause of hypertension (3,4).

The importance of early identifying PA is not only due to its high prevalence but also because patients with PA have a higher risk of cardiovascular morbidity and mortality than patients with primary hypertension (5,6). Inappropriate aldosterone secretion influences cardiovascular disease as well as the effect on renal injury (7-9). Hyperaldosteronism may cause a higher estimated glomerular filtration rate (eGFR) and renal perfusion pressure independent of hypertension via activation of the mineralocorticoid receptor (3,7-9). Higher glomerular hyperfiltration is a functional abnormality in PA and masks the underlying structural renal damage due to the longstanding impact of excessive aldosterone secretion (3,7-11).

Specific treatments alleviate the significant adverse effects of PA on patient outcomes. Treatment with either mineralocorticoid receptor antagonists (MRA) or unilateral adrenalectomy (ADX) for PA resolves hypokalemia, decreases blood pressure and eases the parameters of impaired cardiac and renal function but may paradoxically result in a decline in eGFR (1,8). The medical treatment of PA with MRA is the treatment of choice for idiopathic hyperaldosteronism. Current clinical guidelines on PA recommend ADX for unilateral aldosterone-secreting adenomas based on the studies showing the superiority of ADX over the medical treatment with MR (1,11-16). Although not the optimal treatment choice, MRA may also be used to treat patients with unilateral aldosterone-secreting adenoma who are not a candidates for surgery (17). This study compared the effects of ADX and MRA on clinical and biochemical outcomes in patients with PA.

METHODS

This study was a cross-sectional and retrospective study. In this study, the medical records of the patients diagnosed with PA between 2015 and 2021 were reviewed. Sixty-two patients were diagnosed with PA and had documented long-term follow-up data (>1 year) were recruited for the study. Patients with chronic renal impairment, eGFR <60 mL/min/1.73 m^2, and patients with diabetes mellitus were excluded from the study. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula as published in 2009 (18).

Plasma aldosterone concentration (PAC) and plasma renin activity (PRA) were measured using available kits. PAC and PRA were determined via chemiluminescent immunoassay

technology. The diagnosis of PA was defined in patients with an aldosterone/renin ratio (ARR) of more than 20 and at least one positive result on the confirmatory tests (1). ADX was performed in patients with documented unilateral primary aldosteronism and had the lateralization of the source of the excessive aldosterone secretion. Patients with an age of under 35 years with spontaneous hypokalemia-marked aldosterone excess and unilateral adrenal lesions also underwent surgery even without adrenal venous sampling evaluation. The patient who was unable to undergo surgery was recommended medical treatment with mineralocorticoid antagonists. Spironolactone was started with a dose of 12.5 to 25 mg/d and was titrated to a maximum dose of 100 mg/day, if necessary.

The age and gender of the patients were recorded. Venous blood samples were drawn following overnight fasting. Creatinine, eGFR, potassium, sodium, PAC, PRA, and ARR were recorded at baseline and three months after the treatment with ADX or MRA. The lowest potassium level was recorded before treatment, and those with a serum potassium concentration <3.5 mmol/L were considered hypokalemia.

The percent change of creatinine, eGFR, sodium, and potassium between the levels at pretreatment and the levels three months after the treatments (ADX or MRA) was calculated as [(the level at pretreatment-the level at the third month of treatment)/the level at pretreatment] ×100.

The patients were divided into two groups according to the PA treatment method. Group 1 (n=40) was defined as patients treated with MRA, and group 2 (n=22) was defined as patients who underwent ADX. Groups were compared in terms of creatinine, eGFR, potassium, sodium, PAC, PRA, ARR, presence of hypertension, and hypokalemia. The percentage changes in creatinine, eGFR, sodium, and potassium were also compared between the groups. The patients were also compared separately according to the laboratory findings at baseline and the third month of the treatment in each group. A correlation analysis between the percentage of eGFR changes and the percentage of potassium change with clinical and laboratory parameters was also performed.

This study was approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Researches Ethics Committee with the decision number 2930 (date: 19.03.2021). Procedures were performed according to the ethical standards in the Helsinki Declaration.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0. Categorical variables were defined as frequency and percentage rate, and numerical variables were determined as mean ± standard deviation. The Kolmogorov-Smirnov test assessed the normality of the distribution of the quantitative variables. The Student's t-test was performed for normally distributed numeric variables, and the Mann-Whitney U test was performed for non-normally distributed data for independent group comparison. Wilcoxon signed-rank test was used to evaluate paired differences in the levels before and after the treatment. Correlations were expressed by Pearson's correlation analysis or Spearman's correlation analysis when indicated. A p-value <0.05 was set as statistically significant.

RESULTS

Sixty-two patients (40 female/22 male) with PA were included in the study. The mean age of the whole study group was 54.0±9.9 years. The mean PAC and PRA levels in the whole study group were 40.6±36.6 ng/dL and 0.34±0.22 ng/mL/hour, respectively. Forthy-five patients had adrenal adenoma, and the mean adenoma size was 19.9±8.5 mm. All patients had hypertension at baseline, and 11 (50%) patients with adrenal adenoma had complete clinical success with hypertension without antihypertensive drugs after the treatment with ADX. A decrease in the number of drugs for hypertension was observed in the whole study group. Forthy-one patient had hypokalemia at baseline, and all of them resolved after the treatment with MRA or ADX. The patients were divided into groups according to the PA treatment method. Forty patients were followed up with MRA therapy (group 1), and 22 patients underwent ADX (group 2). PAC, ARR, and patients with hypokalemia at baseline were significantly higher in group 2 than in group 1 (p<0.001, p=0.006, and p=0.011; respectively). While potassium in the third month of the treatment was similar between the groups, potassium at baseline was significantly higher in group 1 than in group 2 (p<0.001). The eGFR levels at the baseline and at the third month of the treatment were similar between the groups. The percentage change in eGFR, sodium, and potassium in group 2 was significantly greater than that in group 1. (p=0.031, p=0.009 and p<0.001; respectively). The group comparison of the patient's clinical and laboratory findings treated with MRA or ADX is presented in Table 1.

The patients were also compared separately in each group for the patient laboratory findings at baseline and the third month of the treatment. While the pretreatment eGFR and sodium levels in both treatment groups were significantly higher than the levels in the third month of the treatment (p<0.001 and p<0.001; respectively), the pretreatment

Table 1. Comparison of the patient's clinical and laboratory findings treated with mineralocorticoid receptor antagonists or unilateral adrenalectomy

n=62	Group 1** (Treated with mineralocorticoid receptor antagonist) n=40	Group 2** (Treated with unilateral adrenalectomy) n=22	p
Female/male (n)	22/18	18/4	0.031
Age (years)	56.05±9.74	50.36±9.57	0.031
Patients with adenoma/without adenoma (n)	23/17	22/0	-
PAC (ng/dL)	26.89±15.25	66.67±49.77	<0.001
PRA (ng/mL/hour)	0.32±0.22	0.37±0.24	NS
ARR	122±109	262±242	0.006
Patients with hypokalemia (n, %)	22 (55)	19 (86)	0.011
Creatinine (mg/dL) (pretreatment)	0.74±0.23	0.77±0.22	NS
eGFR (mL/min) (pretreatment)	97.42±17.74	94.23±21.84	NS
Sodium (mEq/L) (pretreatment)	142.58±2.6	143.09±2.16	NS
Potassium (mmol/L) (pretreatment)	3.57±0.56	3.02±0.56	<0.001
Creatinine (mg/dL) (post-treatment)	0.90±0.27	0.98±0.28	NS
eGFR (mL/min) (post-treatment)	85.41±21.72	75.36±22.24	NS
Sodium (mEq/L) (post-treatment)	140.59±2.60	138.95±2.72	0.037
Potassium (mmol/L) (post-treatment)	4.50±0.47	4.72±0.55	NS
Percent change of the creatinine*	-23.18±28.17	-30.13±26.39	NS
Percent change of the eGFR*	11.59±19.54	20.12±14.85	0.031
Percent change of the sodium*	1.41±2.12	2.88±1.78	0.009
Percent change of the potassium*	-27.98±21.61	-60.44±31.03	<0.001

Data were given as mean ± standard deviation. PAC: Plasma aldosterone concentration, PRA: Plasma renin activity, ARR: Aldosterone/renin ratio, eGFR: Estimated glomerular filtration rate, NS: Non-significant, *[(the level at pretreatment-the level at the third month of treatment)/the level at pretreatment] × 100. **p<0.001 for all paired pre- and posttreatment comparisons in all groups (Wilcoxon test)

creatinine and potassium levels in both treatment groups were significantly lower than the levels in the third month of the treatment (p<0.001 and p<0.001; respectively).

The correlation analysis between the percentage of eGFR changes and the percentage of potassium change with clinical and laboratory parameters in the whole study group is presented in Table 2. Significant positive correlations were observed between the percentage of eGFR and the percentage of potassium change with ARR in the whole study group (r=0.403, p=0.002 and r=0.445, p<0.001; respectively).

DISCUSSION

We evaluated the effect of ADX and MRA treatment on clinical and biochemical outcomes in patients with PA in this study. While ARR and PAC were higher in patients with treated ADX than in the patients with MRA, potassium was lower in the patients with ADX. We also demonstrated that both specific treatments for PA (ADX or MRA) cause a decline in eGFR and sodium and an increase in potassium at the third month of the treatment. Furthermore, the percent change of eGFR, sodium, and potassium was more prominent in ADX than in the MRA treatment.

Table 2. Correlation between the percent change of eGFR and potassium with clinical and laboratory parameters in the whole study group

	Percent change of eGFR*		Percent change of potassium*	
n=62	**r**	**p**	**r**	**p**
Age (years)	0.140	0.282	0.100	0.442
Male gender	-0.157	0.227	-0.149	0.251
PAC (ng/dL)	0.344	0.007	0.490	<0.001
PRA (ng/mL/hour)	-0.100	0.452	-0.097	0.466
ARR	0.403	0.002	0.445	<0.001
Patients with hypokalemia at baseline	0.427	0.001	0.749	<0.001
Patients with adenoma	0.076	0.559	0.419	0.001

Data were given as mean ± standard deviation. PAC: Plasma aldosterone concentration, PRA: Plasma renin activity, ARR: Aldosterone/renin ratio, eGFR: Estimated glomerular filtration rate; *The percent change of eGFR and potassium between the level at pretreatment and the level at the third month of the treatment (mineralocorticoid receptor antagonists or unilateral adrenalectomy)

Previous studies have shown that the decline in eGFR following the treatment of the PA is primarily caused by the alleviation of hyperfiltration due to excessive mineralocorticoid effect (8-11). The decline in eGFR was also shown in both the treatment MRA and ADX in this study, but the percent change of eGFR was more prominent with the ADX than with the MRA treatment. Similar to our results, it was revealed that ADX lowered eGFR more prominent than that MRA (19). It was also shown in this study that ARR was higher, and potassium was lower in patients treated with ADX than in the patients treated with MRA. Thus, the more prominent decrease in eGFR in patients treated with ADX could also be explained by the presence of aldosterone-producing adenomas, more pronounced hypokalemia, and higher aldosterone levels. Aldosterone-induced glomerular hyperfiltration caused by higher aldosterone resolves after treatment and results in a more prominent eGFR decline. Aging causes significant changes in the structure and function of the glomerulus. Recent studies reported that older age was a risk factor for the significant decrease in eGFR in patients treated with ADX or MRA (19,20). Unlike these studies, we did not observe any association between age and eGFR decline in patients treated with ADX or MRA. However, a positive association between eGFR decline with ARR and PAC was also shown in this study. Consistent with our study, there were studies showing that the eGFR decline was greater if aldosterone was higher before treatment (7,20,21). Therefore, we speculate that baseline PAC and ARR may be more important than age for a decline in eGFR.

Hypertension may persist after the PA-specific treatment, and only approximately one-third of such patients normalize blood pressure without the use of any additional medical treatment for hypertension (22). While 50% of the patients treated with ADX did not need any antihypertensive drugs, a decrease in the number of drugs for hypertension was observed in all other patients. These findings suggest that the normalization of hypertension is more pronounced with ADX. It was also shown in another study that low serum potassium levels at baseline were an indicator of a decline in eGFR (7). A similar association was shown between the percentage change in eGFR and patients with hypokalemia in our study. We also evaluated the parameters related to the percent change of potassium with treatment in this study. It was shown that the percent change of potassium was associated with pretreatment PAC and adrenal adenoma existence. Furthermore, more hypokalemia was observed in patients treated with ADX, and post-treatment normokalemia was detected in all patients treated with both ADH and MRA.

There are some limitations to the present study. First, our study's retrospective and single-center design with a relatively small patient number may have affected the results of the study. Secondly, patients treated ADX had a more pretreatment biochemical severity of PA than those treated with MRA, which may impact our clinical results.

CONCLUSION

ADX and MRA treatments could provide the amelioration of renal function, resolve hypertension and normalize potassium levels in patients with PA. Aldosterone-induced glomerular hyperfiltration in PA resolves after both ADX and MRA treatments and results in a more prominent eGFR decline, especially in patients treated with ADX. These findings suggest that all patients should be carefully evaluated for the feasibility of ADX therapy. Moreover, MRA could be considered as an effective treatment option, especially for patients not candidates for ADX. Therefore,

physicians should be aware of evaluating the renal function after the treatment because pretreatment eGFR alone may not be a good predictor of renal function. The early detection of renal disease after the treatment is important to prevent adverse outcomes.

ETHICS

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Researches Ethics Committee with the decision number 2930 (date: 19.03.2021). Procedures were performed according to the ethical standards in the Helsinki Declaration.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: S.T., H.P., Design: H.P., Data Collection or Processing: S.T., H.P., Analysis or Interpretation: S.T., H.P., Literature Search: S.T., H.P., Writing: S.T., H.P.

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

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

REFERENCES

1. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016;101:1889-916.
2. CONN JW. Presidential address. I. Painting background. II. Primary aldosteronism, a new clinical syndrome. J Lab Clin Med 1955;45:3-17.
3. Young WF Jr. Diagnosis and treatment of primary aldosteronism: practical clinical perspectives. J Intern Med 2019;285:126-48.
4. Hannemann A, Wallaschofski H. Prevalence of primary aldosteronism in patient's cohorts and in population-based studies--a review of the current literature. Horm Metab Res 2012;44:157-62.
5. Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol 2005;45:1243-8.
6. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2018;6:41-50.
7. Kramers BJ, Kramers C, Lenders JW, Deinum J. Effects of Treating Primary Aldosteronism on Renal Function. J Clin Hypertens (Greenwich) 2017;19:290-5.
8. Sechi LA, Novello M, Lapenna R, Baroselli S, Nadalini E, Colussi GL, et al. Long-term renal outcomes in patients with primary aldosteronism. JAMA 2006;295:2638-45.
9. Rossi GP, Bernini G, Desideri G, Fabris B, Ferri C, Giacchetti G, et al. Renal damage in primary aldosteronism: results of the PAPY Study. Hypertension 2006;48:232-8.
10. Reincke M, Rump LC, Quinkler M, Hahner S, Diederich S, Lorenz R, et al. Risk factors associated with a low glomerular filtration rate in primary aldosteronism. J Clin Endocrinol Metab 2009;94:869-75.
11. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Renal Outcomes in Medically and Surgically Treated Primary Aldosteronism. Hypertension 2018;72:658-66.
12. Nishikawa T, Omura M, Satoh F, Shibata H, Takahashi K, Tamura N, et al. Guidelines for the diagnosis and treatment of primary aldosteronism--the Japan Endocrine Society 2009. Endocr J 2011;58:711-21.
13. Velema M, Dekkers T, Hermus A, Timmers H, Lenders J, Groenewoud H, et al. Quality of Life in Primary Aldosteronism: A Comparative Effectiveness Study of Adrenalectomy and Medical Treatment. J Clin Endocrinol Metab 2018;103:16-24.
14. Rossi GP, Maiolino G, Flego A, Belfiore A, Bernini G, Fabris B, et al. Hypertension 2018;71:585-91.
15. Wu VC, Wang SM, Chang CH, Hu YH, Lin LY, Lin YH, et al. Long term outcome of Aldosteronism after target treatments. Sci Rep 2016;6:32103.
16. Arlt W, Lang K, Sitch AJ, Dietz AS, Rhayem Y, Bancos I, et al. Steroid metabolome analysis reveals prevalent glucocorticoid excess in primary aldosteronism. JCI Insight 2017;2:e93136.
17. Lim PO, Young WF, MacDonald TM. A review of the medical treatment of primary aldosteronism. J Hypertens 2001;19:353-61.
18. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
19. Nakamaru R, Yamamoto K, Akasaka H, Rakugi H, Kurihara I, Yoneda T, et al. Age-stratified comparison of clinical outcomes between medical and surgical treatments in patients with unilateral primary aldosteronism. Sci Rep 2021;11:6925.
20. Kobayashi H, Abe M, Nakamura Y, Takahashi K, Fujita M, Takeda Y, et al. Association Between Acute Fall in Estimated Glomerular Filtration Rate After Treatment for Primary Aldosteronism and Long-Term Decline in Renal Function. Hypertension 2019;74:630-8.
21. Tanase-Nakao K, Naruse M, Nanba K, Tsuiki M, Tagami T, Usui T, et al. Chronic kidney disease score for predicting postoperative masked renal insufficiency in patients with primary aldosteronism. Clin Endocrinol (Oxf) 2014;81:665-70.
22. Sawka AM, Young WF, Thompson GB, Grant CS, Farley DR, Leibson C, et al. Primary aldosteronism: factors associated with normalization of blood pressure after surgery. Ann Intern Med 2001;135:258-61.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:316-322
DOI: 10.4274/BMJ.galenos.2022.2022.4-12

Research

Attitudes and Seropositivity Rates of Healthcare Workers for CoronaVac® During the COVID-19 Pandemic in a Pediatric Department

Bir Pediatri Departmanında COVİD-19 Pandemisi Sırasında CoronaVac® Aşısı için Sağlık Çalışanlarının Tutumları ve Seropozitiflik Oranları

Nihal Akçay[1], Mehmet Emin Menentoğlu[1], Canan Baydemir[2], Esra Şevketoğlu[1]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, İstanbul, Turkey
[2]Kocaeli University Faculty of Medicine, Department of Biostatistics, Kocaeli, Turkey

ABSTRACT

Objective: Healthcare workers (HCWs) are known be at a high risk of transmission during the coronavirus disease-2019 (COVID-19) pandemic. The present study evaluated HCWs' attitudes toward COVID-19 vaccines, and COVID-19 serologic status before and after the vaccination.

Methods: This study is a prospective observational study. All participants completed a brief survey and were questioned about their intentions and hesitations about getting CoronaVac®. Before the CoronaVac® vaccine, the anti-body levels of all participants were checked. For those who agreed to get the vaccine, in the second step of the study, anti-body titers were checked twice: 1 month after the 1st and the 2nd doses of vaccination. In the last step of the study, COVID-19 surveillance was performed on all participants for 6 months.

Results: A total of 127 participants, 104 females, and 23 males, with a median age of 29 years were included in the study. A total of 43 HCWs had a positive history of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the most affected group was physicians (41.8%) followed by nurses (27.6%). Among 43 participants who had COVID-19 history positive, 31 of them tested positive for anti-bodies, while 12 of them were negative. Anti-body levels were tested as positive in 4 of 84 participants who had no positive history of COVID-19. Seventy-six (59.8%) were vaccinated. The reasons for vaccine hesitancy were; a previous infection with the SARS-CoV-2 (n=15, 29.4%), and the belief in vaccine ineffectiveness (n=22, 43.1%). Anti-body response rates were 80.2% after 1st dose and 100% after 2nd dose. In the 6-month follow-up period, unvaccinated 7 (13.7%) HCWs and vaccinated 1 (1.3%) HCW had COVID-19 infections.

Conclusion: Vaccination is essential in terms of protection from COVID-19. CoronaVac® provides an adequate anti-body response rate among HCWs. Vaccine hesitancy against COVID-19 can be a barrier to ending the pandemic in communities. HCWs work also advocates for patients and the public. It is essential to make the HCWs competent with in-service training on vaccines, vaccination, and against vaccine hesitancy.

Keywords: CoronaVac®, COVID-19, healthcare workers, vaccine

ÖZ

Amaç: Sağlık çalışanlarının (SÇ) koronavirüs hastalığı-2019 (COVİD-19) pandemisi sırasında yüksek bulaşma riski altında oldukları bilinmektedir. Bu çalışmanın amacı, SÇ'nin COVİD-19 aşılarına yönelik tutumlarını, aşılama öncesi ve sonrasında COVİD-19 serolojik durumlarını değerlendirmektir.

Gereç ve Yöntem: Bu çalışma prospektif gözlemsel bir çalışmadır. Tüm katılımcılar gerekli anketi doldurdu, CoronaVac® alma konusundaki niyetleri ve tereddütleri hakkında sorgulandı. CoronaVac® aşısından önce tüm katılımcıların antikor seviyeleri kontrol edildi. Aşı olmayı kabul edenler, çalışmanın ikinci aşamasında, birinci ve ikinci doz aşıdan 1 ay sonra olmak üzere iki kez antikor titreleri kontrol edildi. Çalışmanın son aşamasında tüm katılımcılara 6 ay boyunca COVİD-19 sürveyansı yapıldı.

Bulgular: Çalışmaya 104'ü kadın ve 23'ü erkek olmak üzere, ortanca yaşı 29 olan toplam 127 katılımcı dahil edildi. Toplam 43 sağlık çalışanında pozitif şiddetli akut solunum sendromu koronavirüs-2 (SARS-CoV-2) enfeksiyonu öyküsü vardı; çok etkilenen grup doktorlar (%41,8) ve sonrasında hemşirelerdi (%27). COVİD-19 öyküsü pozitif olan 43 katılımcıdan 31'inin antikor testi pozitif, 12'si negatif çıktı. COVİD-19 geçirme öyküsü

Address for Correspondence: Nihal Akçay, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, İstanbul, Turkey
Phone: +90 212 414 73 29 E-mail: drnihalakcay@gmail.com ORCID ID: orcid.org/0000-0002-8273-2226

Cite as: Akçay N, Menentoğlu ME, Baydemir C, Şevketoğlu E. Attitudes and Seropositivity Rates of Healthcare Workers for CoronaVac® During the COVID-19 Pandemic in a Pediatric Department. Med J Bakirkoy 2022;18:316-322

Received: 13.04.2022
Accepted: 25.07.2022

olmayan 84 katılımcıdan 4'ünün antikoru pozitif bulundu. Tüm katılımcıların 76'sı (%59,8) aşılanmıştır. Aşı tereddüt nedenleri; geçirilmiş SARS-CoV-2 enfeksiyonu (n=15, %29,4) ve aşının etkisiz olduğunun düşünülmesi (n=22, %43,1) olarak bildirilmiştir. Antikor yanıt oranları, 1. doz aşıdan sonra %80,2 ve 2. doz aşıdan sonra %100 saptandı. Altı aylık takip döneminde, aşılanmamış 7 (%13,7) ve aşılı 1 (%1,3) sağlık çalışanı COVİD-19 enfeksiyonu geçirdi.

Sonuç: COVİD-19'dan korunmak için aşılamak esastır. CoronaVac®, sağlık çalışanlarında yeterli antikor yanıtı sağlamaktadır. COVİD-19'a karşı aşı tereddütü, toplumların pandemiyi sonlandırmasında bir engel olabilir. Sağlık çalışanları, hastalar ve halk için örnek teşkil etmektedirler. Sağlık çalışanlarının aşı, aşılanma ve aşı tereddütüne karşı hizmet içi eğitimlerle yetkin hale getirilmesi önemlidir.

Anahtar Kelimeler: CoronaVac®, COVİD-19, sağlık çalışanları, aşı

INTRODUCTION

Healthcare workers (HCWs) take an active role in the diagnosis, treatment, and monitoring stages of coronavirus disease-2019 (COVID-19). During the pandemic process, HCWs need extra care in vaccination from other occupational groups because they carry the risk of being infected, getting the disease, transmission, and even dying. The number of HCWs who have been diagnosed with this disease and lost their lives due to COVID-19 is increasing day by day worldwide (1). Rapid and safe protection of HCWs with vaccination is one of the most important elements in the control of an epidemic (2). Vaccination against the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) in Turkey started for HCWs as a prioritized group, on January 14, 2021. Afterward, the risk groups were expanded and community vaccination was initiated (3). SARS-CoV-2 vaccines (COVID-19 vaccines) are considered the most promising approach to ending the pandemic. CoronaVac® (Sinovac, China), inactivated SARS-CoV-2 vaccine, in which the vast majority of HCWs are vaccinated in our country, is well-tolerated and induced an anti-body response in phase 1 and 2 studies (4).

We determined COVID-19 immunity among HCWs and their opinions on COVID-19 vaccines. We also assessed the seropositivity rates after CoronaVac® vaccination in the study group and the surveillance of the COVID-19 was performed among those for 6 months.

METHODS

Design and Setting

The study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2021-03-14, date: 01.02.2021). This study is a prospective observational study, conducted to obtain the anti-body levels for SARS-CoV-2 before the CoronaVac® (Sinovac, China) vaccination of the people who are working as HCWs in the pediatric emergency room (PER) and pediatric intensive care unit (PICU) in Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey. The participants, including physicians, nurses, and other medical staff, were enrolled in the study between 1 and 14 January 2021. Participants were informed about all the steps of the study. Being a worker in the PER, PICU, and being 18 years and older were inclusion criteria. HCWs who had consent and were eligible for the study were included in the study. HCWs who had not worked in PICU and PER, or who did not give a written informed consent form were excluded. One hundred and sixty-eight HCWs were working in these departments and 127 HCWs were eligible to join the study (Figure 1).

In the first step, all participants completed a brief survey, and a blood sample was obtained to detect the anti-body levels against SARS-CoV-2. Survey data; included demographics, medical history, profession, experience in the profession, COVID-19 history, dates, and results of COVID-19 Polymerase Chain Reaction tests, and family diagnosis of COVID-19. Additionally, all participants were questioned about their intentions regarding COVID-19 vaccinations. HCWs who volunteered to be vaccinated were vaccinated with CoronaVac® (Sinovac, China) vaccine.

In the second step of the study, those who had CoronaVac®, anti-body titers were checked two more times: 1 month after 1st and the 2nd doses of vaccination. After all, vaccinations, the information about possible side effects was given and one week after each vaccination, appointments (by phone or face-to-face interview) were planned.

As strict infection control measures, HCWs were monitored for COVID-19 in pediatric department. In the last step of the study, COVID-19 surveillance was performed on all participants for 6 months (Figure 1).

Serum Samples

Approximately 10 mL of venous blood was collected from the subjects included in the study. Serum was separated by centrifugation at 5,000 rpm for five minutes within two hours after blood collection. The serum samples were tested for anti-SARS-CoV-2 anti-bodies on the same day. Increased serum samples were stored in Eppendorf tubes at -20 °C as 1.5 mL aliquots. The same procedure was repeated 28 days after the 1st vaccine and 28 days after the 2nd vaccine in the vaccinated participants. The study flowchart is given in Figure 1.

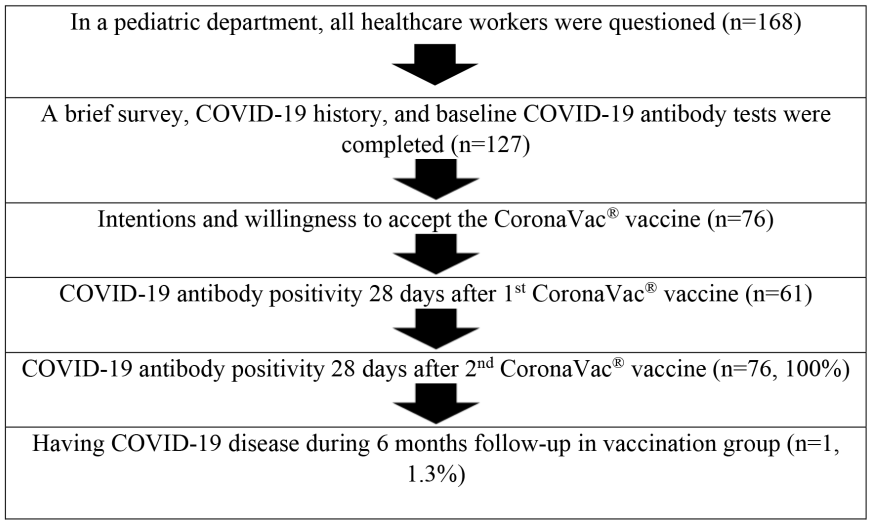

Figure 1. Flowchart of the study
COVID-19: Coronavirus disease-2019

Serological Tests

All tests were performed at the Department of Laboratory Medicine, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey. Blood samples were processed and stored, as noted previously. Total anti-bodies against SARS-CoV-2 were detected using the Elecsys® anti-SARS-CoV-2 immunoassay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) on a Cobas e801 analyzer. A cut-off index >1 is positive.

In the case of positivity, a second test with Elecsys® anti-SARS-CoV-2 S immunoassay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) on a Cobas e801 analyzer for anti-bodies was performed to confirm the results. A cut-off index >0.8 is positive. Anti-body levels were performed using the Elecsys® anti-SARS-CoV-2 S immunoassay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) after the 1st and 2nd vaccinations of the vaccinated participants.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov tests were used to test the normality of data distribution. Continuous variables were expressed as mean ± standard deviation, median (25th-75th percentiles), and categorical variables were expressed as counts (percentages). Differences between groups were tested with the Mann-Whitney U test for numerical variables that did not have a normal distribution also Pearson's, Yates chi-square Fisher Exact and Monte Carlo chi-square analyses were used for categorical variables. $P<0.05$ was considered statistically significant for significance.

RESULTS

A total of 127 HCWs were enrolled in the study (Figure 1). In all, 104 (81.9%) of these responders were women, and 23 (18.1%) were men. The median age of HCWs was 29 years [Interquartile range (IQR): 27-34 years] and the median professional experience was 4 years (IQR: 3-7 years). Participants included 61 (48%) physicians, 49 (38.6%) nurses, 12 (9.4%) cleaning staff, and 5 (3.9%) secretaries. For health status, 26 (20.5%) of them reported having comorbidities, 22 (17.3) continually used medications and 36 (28.3%) of them reported tobacco usage. The median body mass index of HCWs was 23 kg/m^2 (IQR: 20.8-25.3 23 kg/m^2). In all, 8 (6.2%) of them had obesity, 3 (2.3%) of them had morbid obesity, and 28 (22%) of them were overweight (Table 1). In terms of transportation, 59 (46.5%) HCWs used public transportation whereas 51 (40.2%) used private cars, and 17 (13.4%) came to the hospital by walking. Only 3 (2.4%) participants had a history of traveling to abroad. The median number of people living in the same house with HCWs was 2 (IQR: 2-4) (Table 1).

Previous COVID-19 history was detected among 43 (33.8%) participants. The history and seropositivity rates are given in Table 2. Among healthcare workers, physicians were the most affected group (n=18, 41.8%), followed by nurses (n=13, 27.6%). Of those who had COVID-19 history, 33 (76.7%) HCWs were the index cases in their houses. Anti-body levels were tested as positive in 4 (4.8%) of 84 participants who had no positive history of COVID-19. In all study groups, the CoronaVac® acceptance rate was 59.8%. The distribution of vaccination rates among different serologic groups is given in Table 2.

Table 1. Demographic characteristics of the participants

	All participants (127)	COVID-19 history + participant (43)	COVID-19 history -participant (84)	p-value
Age, median years (IQR)	29 (27-34)	29 (27-36)	28.5 (27-33)	0.480
Gender, female, n (%)	104 (81.9)	39 (90.7)	65 (77.4)	0.109
Specialty				
Physician, n (%)	61 (48)	18 (41.8)	43 (51.2)	
Nurse, n (%)	49 (38.6)	13 (27.6)	36 (42.8)	0.006
Cleaning staff, n (%)	12 (9.4)	8 (18.6)	4 (4.8)	
Secretary, n (%)	5 (3.9)	4 (9.3)	1 (1.2)	
Professional experience median years (IQR)	4 (3-7)	5.5 (3-7)	4 (2-7.75)	0.167
Comorbidity, n (%)	26 (20.5)	11 (25.6)	15 (17.9)	0.430
Chronic medications, n (%)	22 (17.3)	8 (18.6)	14 (16.7)	0.980
BMI median (IQR)	23 (20.8-25.3)	23 (20.9-27)	22.7 (20.4-25)	0.434
BMI <18	5 (3.9)	2 (4.7)	3 (3.6)	
18-24.99	84 (66.1)	26 (60.5)	58 (69)	
25-29.99	27 (21.3)	11 (25.6)	16 (19)	0.664
30-39.99	8 (6.3)	2 (4.7)	6 (7.1)	
>40	3 (2.4)	2 (4.7)	1 (1.2)	
History of traveling abroad, n (%)	3 (2.4)	-	3 (3.6)	0.550
How to reach the hospital?				
Public transport, n (%)	59 (46.5)	20 (46.5)	39 (46.4)	0.778
Own car, n (%)	51 (40.2)	16 (37.2)	35 (41.7)	
Walking, n (%)	17 (13.4)	7 (16.3)	10 (11.9)	
Number of the people at the same home, median (IQR)	2 (2-4)	3 (2-4)	2 (2-3)	0.003
Number of the COVID-19 test (PCR), median (IQR)	5 (3-8)	6 (4-9)	5 (3-8)	0.032
Will you get the COVID-19 vaccine?				
Yes, n (%)	76 (59.8)	22 (51.2)	54 (64.3)	0.216
No, n (%)	51 (40.2)	21 (48.8)	30 (35.7)	
Why don't you get the COVID-19 vaccine?				
Have had a COVID-19 infection, n (%)	15 (11.7)	14 (32.5)	1 (1.1)	
Thinks the vaccine will be ineffective, n (%)	22 (17.3)	5 (11.6)	17 (20.2)	<0.001
Fear of side effects, n (%)	5 (3.9)	0 (0.0)	5 (5.9)	
Pregnancy or breastfeeding, n (%)	6 (4.6)	2 (4.6)	4 (4.7)	
Fear of allergies, n (%)	3 (2.3)	0 (0.0)	3 (3.5)	

BMI: Body mass index, COVID-19: Coronavirus disease-2019, IQR: Interquartile range, PCR: Polymerase chain reaction

The participants who refused vaccinations were questioned. The distribution of their reasons is given in Table 1. Fifteen (29.4%) HCWs expressed they already had the disease, 22 (43.1%) thought the vaccine was ineffective, and 5 (9.8%) of them expressed that they had concerns about its side effects. Three (5.8%) HCWs had doubts about allergic reactions, and 6 (11.8%) women refused to get the vaccine because they were pregnant or breastfeeding.

The side effects seen in individuals who were vaccinated were as follows: pain at the injection site (n=21, 27.6%),

Table 2. Summary of findings in the study

Previous history of COVID-19 disease with PCR positivity	Yes (n=43)				No (n=84)			
SARS-CoV-2 antibody (ab) results	Positive (n=31)		Negative (n=12)		Positive (n=4)		Negative (n=80)	
CoronaVac® vaccine acceptance (1st dose)	Yes (n=15)	No (n=16)	Yes (n=7)	No (n=5)	Yes (n=2)	No (n=2)	Yes (n=52)	No (n=28)
SARS-CoV-2 ab positivity 28 days after 1st CoronaVac® vaccine, n (%)	15 (100%)	NA	6 (85.7%)	NA	2 (100%)	NA	38 (73%)	NA
SARS-CoV-2 ab positivity 28 days after 2nd CoronaVac® vaccine, n (%)	15 (100 %)	NA	7 (100%)	NA	2 (100%)	NA	52 (100%)	NA
Having COVID-19 disease during 6 months follow-up, n (%)	None	None	None	1 (20%)	1 (50%)	None	None	6 (21%)

COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, NA: Not applicable

myalgia (n=12, 15.7%), fatigue (n=12, 15.7%), headache (n=4, 5.2%) and fever (n=3, 3.9%). No life-threatening side effects or allergic reactions were observed. COVID-19 anti-body positivity rate was 80.2% among all participants 28 days later than the administration of the first vaccine. This rate exceeded 100% after the administration of the second CoronaVac® vaccine. The distribution of seropositivity rates is given in Table 2. During the 6-month follow-up period, 7 (13.7%) unvaccinated HCWs had COVID-19 infections. One of them had a history of previous COVID-19 infection. Only 1 (1.3%) HCW had COVID-19 after 2 doses of CoronaVac® when we investigated that case, she was working as a chief physician in PICU for longer hours than usual due to overload.

DISCUSSION

In this study, we report the incidence of contracting COVID-19 infection, the attitudes, and seropositivity rates of HCWs for CoronaVac® in a pediatric department.

The rate of COVID-19 infections in HCWs is higher than that results in the general population (5,6). During the first 10 months of the pandemic, more than 30% of the HCWs who participated in our study had COVID-19 infection. In our study, among 127 participants, 43 (33.8%) of them had a positive history of SARS-CoV-2, and 4 (3.1%) of them had anti-body-positivity had a negative history of SARS-CoV-2 to the disease, some people can have the infection without any symptoms, but still they might spread it (7). Thus, the vaccination of HCW is essential in the control of the infection measures through the population (2).

When a new vaccine is introduced, vaccine hesitancy may raise (8). Indeed, the World Health Organization has considered the concept of vaccine hesitancy as one of the top ten threats to global health (9). In this study, it was observed that nearly 40% HCWs were vaccine-hesitant. A review examined the HCWs' vaccine perceptions, knowledge and vaccination practices in 34 countries. It was stated that HCW are vital advocates for patients and the public, but studies indicated a prevalence of provider hesitancy about inadequate knowledge, low vaccine confidence, and suboptimal uptake themselves (10). There are many studies that have compared vaccine acceptance in different populations. Vaccine acceptance rates differ between occupational groups. Physicians are the occupational group most likely to accept vaccination also nurses are less often vaccine acceptors than physicians (11,12). In a study, which was held online in France in February 2021, the acceptance of the COVID-19 vaccine was examined among HCWs. In the 1965 HCWs, 1436 (73.1%) declared vaccine acceptance, 453 (23.1%) had vaccine hesitations and 76 (3.9%) of them stated that they were against vaccination (13). In another study conducted in France, among 2,057 healthcare professionals (21% physicians, 24% pharmacists, 18% nurses, 10% assistant nurses, 27% other); 1,554 (76.9%) declared that they would have the COVID-19 vaccine. Nurses and assistant nurses were found to be less willing than doctors to accept the vaccine against COVID-19 (14). In Israel, 1,941 people participated in an online study to compare the attitudes between the general population and health workers against COVID-19 vaccines. It has been observed

that healthcare personnel caring for COVID-19-positive patients and individuals who consider themselves at risk of illness are willing to vaccinate with COVID-19 whenever possible. In contrast, parents, nurses, and HCWs who did not encounter SARS-CoV-2 positive patients expressed higher levels of vaccine hesitancy (11). In our study, the incidence of COVID infection among physicians was 29.5%, while it was 37.9% among non-physician HCWs. Although all participants were involved in the care of SARS-CoV-2-positive children, the vaccination rate was 72.1% among doctors, and 48.5% among non-physician HCWs. Efforts are recommended to inform healthcare professionals about the benefits of COVID-19 vaccines to maintain high vaccination rates. It is essential to make HCW competent with in-service training on vaccine education and their own vaccine acceptance (10).

According to the phase 3 results of CoronaVac® performed in Brazil, Chile, and Turkey, while no serious side effects were observed after vaccination, the most common side effects are fatigue, headache, myalgia, fever, chills, and pain at the injection site. It was reported that no life-threatening side effects were observed in the phase 2 data, all side effects were seen between 25 and 35% of the subjects in the groups, and the most common side effect was pain at the injection site (15-17). In our study, the most common side effect was pain at the injection site and no life-threatening side effects were observed. Since the protection of vaccines is due to the complex interaction of the innate humoral and cellular immune response, the anti-body response is considered an important indicator of the immune response, although it does not fully demonstrate the protection of the vaccine (18). In our study, the ability of CoronaVac® to produce anti-bodies was found to be 100% at least 28 days after the second vaccine.

There are some limitations to our study. Though the study was conducted in a certain occupational group, the results cannot be generalized to the population and all socioeconomic strata of society. The side effects were based on the reports of individuals. The humoral (neutralizing anti-body) response of the vaccine was revealed with anti-body measurements; no information on cellular immunity was presented. Therefore, this study cannot provide sufficient evidence on the protection of individuals from COVID-19.

CONCLUSION

In conclusion, vaccination of HCWs who are dealing with COVID-19 patients is essential to protect themselves and the population around them. Vaccine hesitancy against COVID-19 is a barrier to ending the pandemic in communities. It is recommended to identify the groups where vaccine acceptance is low or hesitant and to take additional precautions for these groups.

ETHICS

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2021-03-14, date: 01.02.2021).

Informed Consent: Written informed consent to publication has been obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: N.A., Concept: N.A., E.Ş., Design: N.A., E.Ş., Data Collection or Processing: N.A., M.E.M., Analysis or Interpretation: N.A., M.E.M., C.B., Literature Search: N.A., E.Ş., Writing: N.A., E.Ş.

Conflicts of Interest: The authors declared that they have no conflicts of interest.

Financial Disclosure: This study received financial support from Bakirköy Dr. Sadi Konuk Training and Research Hospital Education Committee.

REFERENCES

1. Gómez-Ochoa SA, Franco OH, Rojas LZ, Raguindin PF, Roa-Diaz ZM, Wyssmann BM, et al. COVID-19 in Health-Care Workers: A Living Systematic Review and Meta-Analysis of Prevalence, Risk Factors, Clinical Characteristics, and Outcomes. Am J Epidemiol 2021;190:187.
2. Barranco R, Ventura F. Covid-19 and infection in health-care workers: An emerging problem. Med Leg J 2020;88:65-6.
3. T.C. Sağlık Bakanlığı COVID-19 Aşısı Bilgilendirme Platformu. [cited 2021 Apr 27]. https://covid19asi.saglik.gov.tr/TR-77706/covid-19-asisi-ulusal-uygulama-stratejisi.html (Accessed date: 2 Apr 2021).
4. Wu Z, Hu Y, Xu M, Chen Z, Yang W, Jiang Z, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021;21:803-12.
5. The impact of COVID-19 on health and care workers: a closer look at deaths. [Internet]. [cited 2021 Sep 20]. Available at https://apps.who.int/iris/bitstream/handle/10665/345300/WHO-HWF-WorkingPaper-2021.1-eng.pdf
6. Nguyen LH, Drew DA, Joshi AD, Guo CG, Ma W, Mehta RS, et al. Risk of COVID-19 among frontline healthcare workers and the general community: a prospective cohort study. Preprint. medRxiv. 2020 May 15.
7. Gao Z, Xu Y, Sun C, Wang X, Guo Y, Qiu S, et al. A systematic review of asymptomatic infections with COVID-19. J Microbiol Immunol Infect 2021;54:12-6.
8. Puri N, Coomes EA, Haghbayan H, Gunaratne K. Social media and vaccine hesitancy: new updates for the era of COVID-19 and globalized infectious diseases. Hum Vaccin Immunother 2020;16:2586-93.
9. WHO Ten threats to global health in 2019. Available at: https://www.who.int/news-room/spotlight/ten-threats-to-globalhealth-in-2019. [accessed 2021 July 6].

10. Lin C, Tu P, Beitsch LM. Confidence and Receptivity for COVID-19 Vaccines: A Rapid Systematic Review. Vaccines (Basel) 2020;9:16.
11. Dror AA, Eisenbach N, Taiber S, Morozov NG, Mizrachi M, Zigron A, et al. Vaccine hesitancy: the next challenge in the fight against COVID-19. Eur J Epidemiol 2020;35:775-9.
12. Recensement national des cas de COVID-19 chez les professionnelsene´tablissements de sante´ n.d. Available at: https://www.santepubliquefrance.fr/etudes-et-enquetes/recensement-national-des-cas-de-covid-19-chez-lesprofessionnels-en-etablissements-de-sante. (Accessed date: 1 june 2022)
13. Paris C, Bénézit F, Geslin M, Polard E, Baldeyrou M, Turmel V, et al. COVID-19 vaccine hesitancy among healthcare workers. Infect Dis Now 2021;51:484-7.
14. Gagneux-Brunon A, Detoc M, Bruel S, Tardy B, Rozaire O, Frappe P, et al. Intention to get vaccinations against COVID-19 in French healthcare workers during the first pandemic wave: a cross-sectional survey. J Hosp Infect 2021;108:168-173.
15. Palacios R, Batista AP, Albuquerque CSN, González Patiño E, Santos JP, Pessoa-Conde MTR, et al. Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: The PROFISCOV study (preprint). DOI: 10.2139/ssrn.3822780
16. Bueno SM, Abarca K, González PA, Gálvez NMS, Soto JA, Duarte LF, et al. Safety and Immunogenicity of an Inactivated Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine in a Subgroup of Healthy Adults in Chile. Clin Infect Dis 2022;75:e792-e804.
17. Akova M, Unal S. A randomized, double-blind, placebo-controlled phase III clinical trial to evaluate the efficacy and safety of SARS-CoV-2 vaccine (inactivated, Vero cell): a structured summary of a study protocol for a randomised controlled trial. Trials 2021;22:276.
18. Zimmermann P, Curtis N. Factors That Influence the Immune Response to Vaccination. Clin Microbiol Rev 2019;32:e00084-18.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:323-329
DOI: 10.4274/BMJ.galenos.2022.2022.7-9

Research

Efficacy and Safety of Microscopic Bilateral Decompression with Unilateral Laminectomy in Geriatric Lumbar Spinal Stenosis Surgery

Lomber Spinal Stenoz Cerrahisinde Unilateral Laminektomi ile Bilateral Dekompresyon Yaklaşımının Yaşlı Hastalarda Etkinlik ve Güvenilirliği

Doğan Güçlühan Güçlü[1], Duygu Dölen[2]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Neurosurgery, İstanbul, Turkey
[2]İstanbul University, İstanbul Faculty of Medicine, Department of Neurosurgery, İstanbul, Turkey

ABSTRACT

Objective: To evaluate the efficacy and reliability of microscopic bilateral decompression with unilateral laminectomy in geriatric lumbar spinal stenosis (LSS) patients and to compare the results with the younger patients.

Methods: LSS patients who underwent micro-bilateral decompression with a unilateral approach (BiDUA) between May 2015 and June 2019 at (blinded) were retrospectively reviewed. Patients demographic characteristics, pre- and postoperative clinical and radiological features, pain scores and surgical details were evaluated. They were also grouped according to their age to compare the surgical efficacy and reliability in different age groups.

Results: Fifty seven patients were included in our study. There were 28 males and 29 females. Mean age was 65.75±8.96 (46-82). Thirty one (54.4%) patients were 66 years or older. All patients complained of lower back pain and exhibited neurogenic claudication. Twenty nine patients (50.9%) received single-level, whereas 28 patients (49.1%) required double-level surgery. All patients's neurogenic claudication-improved postsurgery. Nine patients experienced postoperative complications (5 dural injuries, 3 superficial wound infections and 1 cerebrospinal fluid fistula). There were statistically significant differences in both back pain and leg pain following surgery. However, there were no statistically significant differences in either visual analog scale back pain or leg pain scores between the age groups.

Conclusion: Although the surgical treatment of LSS involves greater risks in elderly patients, we found no statistically significant difference in the complication rate between age groups following micro-BiDUA, which supports the efficacy and safety of micro-BiDUA for elderly patients.

Keywords: Lumbar stenosis, bilateral decompression with unilateral approach, microsurgery, neurogenic claudication, minimally invasive spine surgery

ÖZ

Amaç: Mikroskobik unilateral laminektomi ile bilateral dekompresyonun geriatrik lomber dar kanal (LSS) hastaların tedavisindeki güvenilirliği ve etkinliğinin araştırılması ve sonuçların genç hastalar ile kıyaslanmasıdır.

Gereç ve Yöntem: Mayıs 2015 ve Haziran 2019 arasında (blinded) mikroskobik unilateral laminektomi ile bilateral dekompresyon (BiDUA) uygulanan LSS hastaları retrospektif olarak incelendi. Hastaların demografik özellikleri, pre ve postoperatif klinik ve radyolojik özellikleri, ağrı skorları ve cerrahi detayları araştırıldı. Hastalar aynı zamanda yaşlarına göre gruplandırılarak farklı yaş grupları arasındaki cerrahi etkinlik seviyeleri karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen 57 hastanın 28'i erkek 29'u kadındı. Ortalama yaş 65,75±8,96 (46-82) olarak hesaplandı. Otuz bir (%54,4) hasta 66 yaş ve üzeriydi. Tüm hastaların bel ağrısı ve nörojenik kladikasyosu mevcuttu. Yirmi dokuz hasta (%50,9) tek seviye, 28 hasta (%49,1) çift seviye nedeniyle opere edildi. Tüm hastaların nörojenik kladikasyosunun ameliyat sonrasında düzeldiği izlendi. Dokuz hastada komplikasyon gelişti (5 dura yaralanması, 3 yüzeyel yara yeri enfeksiyonu ve 1 beyin omurilik sıvısı fistülü). Ameliyat sonrası dönemde hastaların hem bel hem de bacak

Address for Correspondence: Duygu Dölen, İstanbul University, İstanbul Faculty of Medicine, Department of Neurosurgery, İstanbul, Turkey
Phone: +90 537 717 42 40 E-mail: dolenduygu@gmail.com ORCID ID: orcid.org/0000-0002-6929-4401

Cite as: Güçlü DG, Dölen D. Efficacy and Safety of Microscopic Bilateral Decompression with Unilateral Laminectomy in Geriatric Lumbar Spinal Stenosis Surgery. Med J Bakirkoy 2022;18:323-329

Received: 21.07.2022
Accepted: 01.08.2022

ağrısında istatistiksel olarak anlamlı azalma izlendi. Ancak yaş grupları arasında bel ve bacak ağrısı için belirtilmiş vizüel analog skala skorları karşılaştırıldığında, anlamlı sonuca ulaşılamadı.

Sonuç: LSS cerrahisi yaşı hastalarda daha fazla risk içerse de mikroskobik unilateral laminektomi ile bilateral dekompresyonun komplikasyon oranlarının farklı yaş grupları arasında değişmediği gösterilmiştir. Bu sonuç geriatrik popülasyonda tekniğin güvenilirliği ve etkinliğini desteklemektedir.

Anahtar Kelimeler: Lomber dar kanal, mikroskobik unilateral laminektomi ile bilateral dekompresyon, mikrocerrahi, nörojenik kladikasyon, minimal invaziv spinal cerrahi

INTRODUCTION

Lumbar spinal stenosis (LSS) is defined as narrowing of the spinal canal due to the hypertrophic changes of soft tissues, bony structure, lateral recesses, and (or) neural foramina. It usually develops because of facet and intervertebral joint degeneration, thickening of ligamentous structures, or protrusion of the nucleus pulposus (1). In 1949, Verbiest described the clinical relationship between LSS and neurogenic claudication and LSS with claudication is currently one of the most common indications of spinal surgery due to the growing geriatric population and expectations of sustained quality of life in the old age (2-4).

Shortened walking distance, neurological deficits, restricted daily activity, and failure of conservative treatment are common indications for the surgical treatment of LSS. Total laminectomy combined with medial facetectomy and foraminotomy is recognized as the gold standard in LSS surgery. However, long operation time, excessive tissue damage and bleeding, high risk of mortality and morbidity, and instability following LSS surgery have led surgeons to consider alternative surgical techniques, particularly for the elderly, who are also most vulnerable to these complications. In the recent years, operating microscopes and endoscopes have facilitated the greater use of minimally invasive spinal surgical (MISS) techniques for LSS treatment. The primary goals of these MISS approaches are to reduce tissue damage, speed up recovery time, reduce postoperative pain and complication rates, lower blood loss, prevent instability and allow an early return to daily activities. One MISS technique known to be effective for LSS is bilateral decompression with a unilateral approach (BiDUA), which can be performed under either microscope guidance (micro-BiDUA) or endoscope guidance (endo-BiDUA). Micro-BiDUA was first described by Poletti (5) in 1995 and modified by McCulloch and Young (6) in 1998. In this technique, the dural sac and bilateral nerve roots are decompressed by resection of the contralateral ligamentum flavum from the arc inferior, while preserving the supra- and interspinous ligament complex and the contralateral paraspinal muscles and facet joints (7). Based on the previously published studies, Shamji et al. (8) concluded that MISS procedures are safe and effective for elderly LSS patients and Wada et al. (9) reported that endo-BiDUA was superior to traditional laminectomy.

Wada et al. (9) also compared micro-to endo-BiDUA and found various advantages and disadvantages to each procedure. In this study, we evaluated the efficacy and reliability of micro-BiDUA for geriatric LSS. We hypothesize that the short-term efficacy and complication rates of the micro-BiDUA approach for geriatric patients (older than 65 years) would be equivalent to that for younger patients.

METHODS

Patient Selection

Consecutive LSS patients who received micro-BiDUA between May 2015 and June 2019 (blinded) were considered candidates for this study. Inclusion criteria were radiologically diagnosed LSS by magnetic resonance imaging (MRI) and computed tomography (CT), neurogenic claudication with or without radiculopathy, and nonresponse to conservative treatment for more than three months. Patients who had undergone lumbar fusion for LSS and patients with significant instability due to disk herniation, spinal malignancy, or infection were excluded.

All surgical interventions were performed by a single surgeon (G.G.) to minimize variability. All patients received preoperative physical and neurological examination, lumbar MRI, and CT as well as postoperative lumbar CT. In addition to demographic data, clinical variables such as comorbidities, preoperative American Society of Anesthesiologists (ASA) Physical Status classification, duration of surgery, bleeding volume, surgical level (single- or double-level among L3-4, L4-5, and L5-S1), duration of hospitalization, complication rates, patient satisfaction, and pain scores were assessed. Pain levels were scored from zero to ten using a visual analog scale (VAS) in which zero means no pain and ten means the worst pain imaginable. VAS scores were recorded immediately after surgery and during the first, sixth and twelfth month postoperatively (10).

Patients were subgroups according to the severity of neurogenic claudication (1: 0-50 meters; 2: 50-250 meters; 3: 250-1000 meters; 4: over 1000 meters) both preoperatively and at 12 months post-surgery. Patient satisfaction was

evaluated according to the MacNab classification at 12-month post-surgery as perfect (no pain, no disability to work), good (rare back of leg pain), moderate (occasional pain but cannot continue working), poor (continued pain need for second surgery) (11). Patients were also stratified by age into an older group (≥66 years) and a younger group (≤65 years) for comparison of surgical efficacy and reliability. Ethical approval for this study was obtained from University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Clinical Research Ethics Committee (decision no: 2021-17-07, date: 06.09.2021).

Surgical Method

Patients were placed in the prone position for marking of the relevant level under C-arm fluoroscopy guidance. A posterior midline incision was created, and the paravertebral thoracolumbar fascia was opened unilaterally at the planned level while preserving the functional and anatomical integrity of the contralateral muscles, supra- and interspinous ligaments, and the spinous protrusion of midline structures such as interspinous ligaments and thoracolumbar fascia. Paravertebral muscles were removed one-sided by subperiosteal stripping to expose the medial wall of the facet joint. Then, unilateral hemilaminectomy was performed under surgical microscopy. During hemilaminectomy, only the medial parts of the lamina-exerting pressure on the dural sac and nerve root were removed, while facet joints, which are crucial for spine stabilization, were preserved. The thickened ligamentum flavum was resected from the same side and foraminotomy was performed on the nerve roots compressed behind it. Simultaneously, the intervertebral disc space was monitored for disc fragments. Afterwards, the operating table and microscopy were tilted to an angle allowing a contralateral approach, and contralateral hemilaminectomy, flavectomy and foraminotomy were performed using a high-speed drill and Kerrison rongeurs. A transmedian unilateral approach was started at the inferior line of the midline where the spinous process bonds with the insertion line at the lamina. As the thickened ligamentum flavum was resected, pressure on the dural sac was relieved. Following the release of the thickened flavum, the contralateral side was expanded up to the axillary level of the foramen using Kerrison rongeurs. Bleeding and cerebrospinal fluid (CSF) leakage were checked after the contralateral foramen was checked with a nerve hook. Following hemostasis, a drainage tube was inserted in patients requiring surgery at multiple levels.

Statistical Analysis

SPSS version 18.0 was used for all statistical analyses. Numeric variables are presented as mean ± standard deviation, and categorical variables as a number of observations and percentages (%). Quantitative data were compared by student's t-test or Mann-Whitney U test as indicated, while 12-month postoperative results were compared to baseline conditions using the Mantel-Haenszel test. Back pain before and after surgery (postoperative 1st, 6th and 12th months) was compared by Wilcoxon-marked row tests.

RESULTS

Fifty-seven patients were enrolled in our study, of which 31 (54.4%) were aged 66 years or older and 26 (45.6%) were 65 years or younger. Mean age was 65.75±8.96 (46-82) and the cohort included roughly equal numbers of females and males (28, 49.1% vs. 29, 50.9%). All patients reported lower back and leg pain before surgery and substantial reductions post-surgery as measured by VAS scores (Table 1).

Before surgery, 10 patients (17.5%) exhibited neurogenic claudication between 0 and 50 meters and 47 (82.5%)

Table 1. Visual analog scale for back and leg pain before and after surgery

		VAS scores			
Pain locations		**min**	**max**	**mean**	**SD**
Lower back pain	Preoperative	7	9	7.9772	0.59971
	Postoperative 1st month	2	4	2.7544	0.71418
	Postoperative 6th month	1	4	2.1754	0.60127
	Postoperative 12th month	1	3	1.8947	0.55691
Leg pain	Preoperative	7	9	7.3684	0.55522
	Postoperative 1st month	1	5	2.3860	0.83995
	Postoperative 6th month	1	5	2.0175	0.81265
	Postoperative 12th month	1	5	1.9298	0.75261

SD: Standard deviation, VAS: Visual analog scale, min: Minimum, Max: Maximum

approximately 51-250 meters, while 12 months post-surgery, only 4 (7%) demonstrated neurogenic claudication approximately 51-250 meters, with the remaining patients reporting pain between 250 and 1000 meters (18 patients, 31.6%) or above 1000 meters (35 patients, 61.4%). Before surgery, 39 patients (68.4%) were identified as ASA Physical Status grade I (healthy, lowest risk) and 18 (31.6%) as ASA-II (mild systemic disease). Of the total cohort, 57.9% were diagnosed with hypertension, 22.8% with chronic obstructive pulmonary disease (COPD), 21.1% with diabetes mellitus (DM), and 5.3% with congestive cardiac failure. A stroke history was present in 12.3% of the cases. mean duration of operation was 76.84±21.62 min (50-130 mins), average blood loss during surgery was 59.38±23.20 mL (25-120 mL), and the mean hospital stay was 2.49±2.23 days (1-15 days).

Twenty-nine patients (50.9%) received single-level surgery, 21 (36.84%) at L4-5 and 8 (14.03%) L3-4, while 28 (49.1%) required double level, 23 (40.35%) at L3-4 and L4-5 levels and 5 (8.77%) at L4-5 and L5-S1 levels. Neither preoperative nor 12-month postoperative claudication scores differed between patients requiring single-level or double-level surgery according to the Mantel-Haenszel test ($2\times2x^{2}2=1.850$, p=0.174). Alternatively, the duration of the surgery and average blood loss were significantly higher among patients requiring double level surgery (operation duration: $2\times2x^{2}2=33.403$, p<0.001; average blood loss: $2\times2x^{2}2=36.285$, p<0.001) (Table 2 and 3). The duration of hospitalization was also significantly longer in the double-level surgery group. Among the comorbidities examined, only COPD was significantly associated with the time of hospitalization (Z=2.07 p=0.04).

Nine patients experienced postoperative complications (21.05%), including 5 cases of dural injury (8.85%), 3 of superficial wound infection (5.3%), and one case (1.7%) of CSF fistula (requiring reoperation for repair). Only four patients (7%) reported neuropathic pain postoperatively, and there were no postoperative neurological deficits. Of the 9 patients with complications, the majority were in the double-level subgroup (7 vs. 3) including all cases of dural tears, but the difference in the overall complication rate did not reach statistical significance ($2\times2x^{2}2=0.295$ p=0.148).

There were statistically significant differences in both back pain and leg pain following surgery compared to baseline according to the Wilcoxon-marked row test (back pain: 1st month Z=6.71 p<0.05, 6th month Z=6.74 p<0.05, 12th month z=6.69 p<0.05; leg pain: 1st month Z=6.74 p<0.05, 6th month z=6.66 p<0.05, 12th month Z=6.69 p<0.05). Further, most patients reported good or perfect outcome according to the MacNab classification at 12 months post-surgery, and there was no difference in MacNab class distribution at 12-months post-surgery between patients requiring single- and double-level surgical correction ($2\times2x^{2}2=0.893$, p=0.345) (Table 4 and 5). There was also no statistically significant difference in MacNab class distribution between patients with or without a comorbidity.

Finally, we compared baseline condition and postsurgical outcomes between patient subgrouped according to age (≤65 years and ≥66 years). The distribution of surgical sites differed between groups. In the younger subgroup, L4-5 was the most common level (11 patients, 42.3%), followed by L3-4 and L4-5 (9 patients, 34.61%), L3-4 (4 patients,

Table 2. Comparison of surgical duration between patients requiring single-level and double-level micro-BiDUA

		Surgical duration			Total
		30-60 min	61-90 min	91-130 min	
	Single level	18	11	0	29
	Double level	1	9	18	28
Total		19	20	18	57

micro-BiDUA: Micro-bilateral decompression with a unilateral approach

Table 3. Comparison of average blood loss between patients requiring single-level and double-level micro-BiDUA

		Average blood loss			Total
		1-50 mL	51-100 mL	101-150 mL	
	Single level	27	2	0	29
	Double level	3	24	1	28
Total		30	26	1	57

micro-BiDUA: Micro-bilateral decompression with a unilateral approach

15.38%), and L4-5 and L5-S1 (2 patients, 7.69%), while in the elderly subgroup, L3-4 and L4-5 were the most common (14 patients, 45.16%), followed by L4-5 (10 patients, 32.25%), L3-4 (4 patients, 12.9%) and L4-5 and L5-S1 (3 patients, 9.67%). Nonetheless, there were no statistically significant differences in either VAS back pain or leg pain scores between the groups at any postoperative time as evaluated by Mann-Whitney U test (back pain: 1st month Z=1.38, p=0.17; 6th month: Z=1.47, p=0.14; 12th month: Z=0.59, p=0.56; leg pain: 1st month Z=1.06, p=0.29; 6th month Z=1.06, p=0.29; 12th month Z=0.35, p=0.73). Furthermore: the distribution of MacNab classes at 12 months post-surgery, the duration of the operation, and neurogenic claudication distances did not differ between age groups (MacNab class: Z=0.43, p=0.66; duration of the operation: Z=0.75, p=0.45; preoperative neurogenic claudication distance: $2\times2x^{2}2=1.19$, p=0.27; postoperative neurogenic claudication distance: $2\times2x^{2}2=3.84$, p=0.14).

DISCUSSION

With population aging, there is a growing need for surgical procedures with greater efficacy and reduced complication risks in geriatric patients. Many studies have reported generally favorable outcomes using MISS techniques compared with traditional methods, including among geriatric patients (12,13). For instance, Giannadakis et al. (14) reported better patient satisfaction after micro-BiDUA than after open surgical intervention. In our study, as well, micro-BiDUA proved equally effective and safe for patients older than 65 compared to a younger subgroup, despite the more frequent need for multisegment intervention.

Table 4. Distribution of MacNab classifications at 12 months post-surgery

MacNab class	# of patients	%
Poor	1	1.8
Moderate	8	14
Good	33	57.9
Perfect	15	26.3
Total	57	100

Mean lower back and leg pain VAS scores were marked reduced post-surgery (7.87±0.599 and 7.36±0.555 at baseline vs. 1.89±0.556 and 1.92±0.752 12 months), indicating that the surgical outcome was generally successful. Indeed, patient satisfaction as evaluated by the MacNab classification was 84.2% (57.9% rated good and 26.3% as perfect) and did not differ between patients requiring single- or double-level surgery. Similarly, Hwang et al. (15) found substantial improvements in pain score one year after BiDUA (from 6.91±1.98 to 2.08±1.35) as well as high success rates for both low back pain reduction (83.8%) and leg pain reduction (86.3%) (15). Moreover, Oertel et al. (16) reported that VAS improvement was maintained for 4-10 years (6.91±1.98 before surgery to 2.44±1.60 after surgery). Costa et al. (17) also reported an average change in VAS score from 8.9 to 4.2 and a success rate of 87.9% for lower back pain reduction after 30.3 months of follow-up. However, overall results have varied across cohorts, as Yang et al. (18) reported a satisfaction rate of only 61.9% at 3 years post-surgery among patients of similar age to the current study (64.1±8.9 years).

Nevertheless, the BiDUA approach has demonstrated consistent success in older patients. Weiner et al. (7) reported an 87% reduction in pain at one year follow-up and Shabat et al. (19) reported a satisfaction rate of 76% in patients older than 80 years. Similarly, Hwang et al. (15) found no differences in VAS scores or claudication between younger and older age groups at an average follow-up of 6.5 months after BiDUA. Similarly, Ha et al. (20) found no difference in efficacy between 66 and 75 years and over 75 years age groups one year after BiDUA as measured by VAS scores and MacNab classification. Shamji et al. (21) also concluded that BiDUA is an effective and reliable method for elderly LSS patients.

Papavero et al. (22) reported reduced pain in 83.9% of cases after one-year follow-up and a 92.2% improvement in walking performance. In our study as well, neurogenic claudication distance was improved substantially after surgery. While no patient could walk 250 m without pain at baseline, 18 (31.6%) could walk 250-1000 meters and 35 patients (61.4%) over 1000 meters at one-year post-surgery. In support of similar

Table 5. Distribution of MacNab classifications in single- and double-level surgery cases

		MacNab values				Total
		Poor	Moderate	Good	Perfect	
	Single level	0	3	18	8	29
	Double level	1	5	15	7	28
Total		1	8	33	15	57

efficacy in geriatric patients, we found no differences in VAS scores and severe claudication rate between age groups one year after micro-BiDUA. Antoniadis reported that the cases-benefitting most the following surgery could walk less than 50 meters pain-free at baseline. This increased mobility will undoubtedly enhance patient quality of life (23).

The surgical duration was longer and blood loss was greater among patients requiring multilevel surgery. Nonetheless, all procedures were completed within 130 min and almost all patients lost less than 100-mL blood, underscoring the safety of this procedure. Following multiple level surgeries, routine drainage was introduced to achieve adequate bleeding conrol, which probably increased the duration of hospital stay compared to single-level surgeries (24). Shin et al. (25) found that level of preoperative functionality, presencec of DM, number of operated segments, and ASA grade III influenced mean hospitalization time. However, Tanaka et al. (26) found no difference in surgical success between single and multilevel surgeries if patient selection was conducted carefully. They also found significantly higher blood loss during multisegment surgeries but no difference in blood loss per level as well as longer surgical duration but a shorter duration per level (26). Conversely, Papavero et al. (22) found no differences in total operation time or average blood loss, indicating that BiDUA is a safe and effective method for multilevel LSS, even in high-risk patients. Deyo et al. (27) reported that mortality increased with age and was associated with the presence of comorbidities. However, we found no statistically significant difference in the MacNab classification distribution between patients with and without comorbidities.

Minimally invasive approaches have caused less severe tissue damage, fewer intraoperative complications, and lower blood loss, leading to shorter hospitalization. Ha et al. (20) reported an average hospitalization stay of 8 days after BiDUA and an average blood loss of only 30 mL. Further, surgical durations as short as 20 min, average blood loss of only 50 mL, and mean hospitalization times of only one or two days have been reported, although endocrinological or respiratory system diseases in addition to patient age may extend postoperative hospitalization (28,29). In this study, we found that only COPD had a statistically significant impact on hospitalization duration.

Dural injuries have been reported in 1.1%-12% of BiDUA cases. Similar to previous studies, dural injury was the most frequent complication in our cohort study (8.8%), all of which developed during multilevel surgeries (20,30). Alternatively, incidence did not differ between the age groups. In contrast to dural injury, CSF fistulas are relatively uncommon (incidence of 0%-1.5%) and the only such case was encountered in the current study, again during a multisegment operation (16,22,31). Apart from this case, revision surgery was not required during the early postoperative period. Moreover, no cases of instability or restenosis were encountered. Thus, the total complication rate was at the lower end of the range estimated by Deschuyffeleer et al. (32) across postoperative periods (0%-27%). However, our one-year follow-up is considered short-term. These complications reported after BiDUA may be explained by limited surgical space and difficulty seeing critical structures (29).

Because of the retrospective study design, important factors associated with outcome may have been excluded. Furthermore, the small sample size precluded a detailed comparison of specific complications between the age groups.

CONCLUSION

Although the surgical treatment of LSS involves greater risks in elderly patients, we found no statistically significant difference in the complication rate between age groups following micro-BiDUA. Our study therefore supports the efficacy and safety of micro-BiDUA in elderly patients. Additionally, patients reported high satisfaction even if multiple segments required surgical repair.

ETHICS

Ethics Committee Approval: Ethical approval for this study was obtained from University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Clinical Research Ethics Committee (decision no: 2021-17-07, date: 06.09.2021).

Informed Consent: Retrospective study.

Authorship Contributions

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

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

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

REFERENCES

1. Rompe JD, Eysel P, Zöllner J, Nafe B, Heine J. Degenerative lumbar spinal stenosis. Long-term results after undercutting decompression compared with decompressive laminectomy alone or with instrumented fusion. Neurosurg Rev 1999;22:102-6.

2. Issack PS, Cunningham ME, Pumberger M, Hughes AP, Cammisa FP. Degenerative lumbar spinal stenosis: Evaluation and management. Journal of the American Academy of Orthopaedic Surgeons 2012;20:527-35.
3. VERBIEST H. A radicular syndrome from developmental narrowing of the lumbar vertebral canal. J Bone Joint Surg Br 1954;36-B(2):230-7.
4. Wong Chung-Ting M, Chan Pak-Ho A, Cheung KK. A Prospective Study on the Outcome of Degenerative Lumbar Spinal Stenosis Treated With Open Laminotomy. Journal of Orthopaedics, Trauma and Rehabilitation 2012;16:62-5.
5. Poletti CE. Central lumbar stenosis caused by ligamentum flavum: unilateral laminotomy for bilateral ligamentectomy: preliminary report of two cases. Neurosurgery 1995;37:343-7.
6. McCulloch JA, Young PH. Essentials of spinal microsurgery, editors. Hagerstown: Lippincott-Raven; 1999. DOI: 10.1302/0301-620X.81B2.0810373
7. Weiner BK, Walker M, Brower RS, McCulloch JA. Microdecompression for lumbar spinal canal stenosis. Spine (Phila Pa 1976) 1999;24:2268-72.
8. Shamji MF, Goldstein CL, Wang M, Uribe JS, Fehlings MG. Minimally Invasive Spinal Surgery in the Elderly: Does It Make Sense? Neurosurgery 2015;77 Suppl 4:S108-15.
9. Wada K, Sairyo K, Sakai T, Yasui N. Minimally invasive endoscopic bilateral decompression with a unilateral approach (endo-BiDUA) for elderly patients with lumbar spinal canal stenosis. Minim Invasive Neurosurg 2010;53:65-8.
10. Boonstra AM, Schiphorst Preuper HR, Reneman MF, Posthumus JB, Stewart RE. Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. Int J Rehabil Res 2008;31:165-9.
11. Macnab I. Negative disc exploration. An analysis of the causes of nerve-root involvement in sixty-eight patients. J Bone Joint Surg Am 1971;53:891-903.
12. Kelleher MO, Timlin M, Persaud O, Rampersaud YR. Success and failure of minimally invasive decompression for focal lumbar spinal stenosis in patients with and without deformity. Spine (Phila Pa 1976) 2010;35:E981-7.
13. Schöller K, Alimi M, Cong GT, Christos P, Härtl R. Lumbar Spinal Stenosis Associated With Degenerative Lumbar Spondylolisthesis: A Systematic Review and Meta-analysis of Secondary Fusion Rates Following Open vs Minimally Invasive Decompression. Neurosurgery 2017;80:355-67.
14. Giannadakis C, Solheim O, Jakola AS, Nordseth T, Gulati AM, Nerland US, et al. Surgery for Lumbar Spinal Stenosis in Individuals Aged 80 and Older: A Multicenter Observational Study. J Am Geriatr Soc 2016;64:2011-8.
15. Hwang SW, Rhim SC, Roh SW, Jeon SR, Hyun SJ. Outcomes of unilateral approach for bilateral decompressionof lumbar spinal stenosis: comparison between younger and geriatric patients. Kor J Spine 2008;27:51-7.
16. Oertel MF, Ryang YM, Korinth MC, Gilsbach JM, Rohde V. Long-term results of microsurgical treatment of lumbar spinal stenosis by unilateral laminotomy for bilateral decompression. Neurosurgery 2006;59:1264-9; discussion 1269-70.
17. Costa F, Sassi M, Cardia A, Ortolina A, De Santis A, Luccarell G, et al. Degenerative lumbar spinal stenosis: analysis of results in a series of 374 patients treated with unilateral laminotomy for bilateral microdecompression. J Neurosurg Spine 2007;7:579-86.
18. Yang SM, Park HK, Chang JC, Kim RS, Park SQ, Cho SJ. Minimum 3-year outcomes in patients with lumbar spinal stenosis after bilateral microdecompression by unilateral or bilateral laminotomy. J Korean Neurosurg Soc 2013;54:194-200.
19. Shabat S, Arinzon Z, Folman Y, Leitner J, David R, Pevzner E, et al. Long-term outcome of decompressive surgery for lumbar spinal stenosis in octogenarians. Eur Spine J 2008;17:193-8.
20. Ha S, Hong Y, Lee S. Minimally Invasive Lumbar Spinal Decompression in Elderly Patients with Magnetic Resonance Imaging Morphological Analysis. Asian Spine J 2018;12:285-93.
21. Shamji MF, Mroz T, Hsu W, Chutkan N. Management of Degenerative Lumbar Spinal Stenosis in the Elderly. Neurosurgery 2015;77 Suppl 4:S68-74.
22. Papavero L, Thiel M, Fritzsche E, Kunze C, Westphal M, Kothe R. Lumbar spinal stenosis: prognostic factors for bilateral microsurgical decompression using a unilateral approach. Neurosurgery 2009;65(6 Suppl):182-7.
23. Antoniadis A, Ulrich NH, Schmid S, Farshad M, Min K. Decompression surgery for lumbar spinal canal stenosis in octogenarians; a single center experience of 121 consecutive patients. Br J Neurosurg 2017;31:67-71.
24. Lagman C, Ugiliweneza B, Boakye M, Drazin D. Spine Surgery Outcomes in Elderly Patients Versus General Adult Patients in the United States: A MarketScan Analysis. World Neurosurg 2017;103:780-8.
25. Shin JI, Kim JS, Steinberger J, DiCapua J, Cho SK. Patient Factors Contributing to Prolonged Postoperative Length of Stay and Increased Rate of Readmission After Elective Posterior Cervical Fusion. Clin Spine Surg 2018;31:E55-61.
26. Tanaka N, Nakanishi K, Kamei N, Yamamoto R, Nakamae T, Izumi B, et al. Clinical results of microsurgical bilateral decompression via unilateral approach for lumbar canal stenosis with multiple-level involvement. Eur J Orthop Surg Traumatol 2015;25 Suppl 1:S191-8.
27. Deyo RA, Cherkin DC, Loeser JD, Bigos SJ, Ciol MA. Morbidity and mortality in association with operations on the lumbar spine. The influence of age, diagnosis, and procedure. J Bone Joint Surg Am 1992;74:536-43.
28. Murphy ME, Gilder H, Maloney PR, McCutcheon BA, Rinaldo L, Shepherd D, et al. Lumbar decompression in the elderly: increased age as a risk factor for complications and nonhome discharge. J Neurosurg Spine 2017;26:353-62.
29. Ogden M, Yuksel U, Bakar B, Akkaya S, Kamasak K, Dagli AT. The Effects of Microdecompression on Patients with Lumbar Degenerative Spinal Stenosis with or without Degenerative Spondylolisthesis. Turk Neurosurg 2019;29:205-12.
30. Yüce İ, Kahyaoğlu O, Çavuşoğlu HA, Çavuşoğlu H, Aydın Y. Long-Term Clinical Outcome and Reoperation Rate for Microsurgical Bilateral Decompression via Unilateral Approach of Lumbar Spinal Stenosis. World Neurosurg 2019;125:e465-72.
31. Cavuşoğlu H, Kaya RA, Türkmenoglu ON, Tuncer C, Colak I, Aydin Y. Midterm outcome after unilateral approach for bilateral decompression of lumbar spinal stenosis: 5-year prospective study. Eur Spine J 2007;16:2133-42.
32. Deschuyffeleer S, Leijssen P, Bellemans J. Unilateral laminotomy with bilateral decompression for lumbar spinal stenosis: short-term risks in elderly individuals. Acta Orthop Belg 2012;78:672-7.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:330-335
DOI: 10.4274/BMJ.galenos.2022.2022.6-16

Research

Pediatric Lumbar Microdiscectomy

Pediatrik Lomber Mikrodiskektomi

Doğan Güçlühan Güçlü

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

ABSTRACT

Objective: In this study, we will present you a series of lumbar disc herniation (LDH) cases of pediatric age that we had operated using the microdiscectomy method.

Methods: Nine pediatric patients who underwent surgical treatment with microdiscectomy with the diagnosis of LDH by a single surgeon between July 2013 and December 2018 were followed up for approximately 1 year postoperatively, and postoperative low back and leg pain was evaluated with visual analog scale (VAS) score, and operation satisfaction at 1 year was evaluated with MacNab criteria.

Results: The mean age in our study was 14.6. In our study, five patients were operated from L4-5, four patients from L5-S1. The mean of preoperatif VAS was 8.00±0.70, while the mean of postoperatif VAS was 2.00±0.86. The difference between VAS scores was statistically significant (p=0.007). According to the MacNab score in all of our patients, recovery was evaluated as well and excellent.

Conclusion: Microdiscectomy is a safe and effective treatment for pediatric LDH.

Keywords: Microdiscectomy, pediatric lumbar disc herniation, MacNab

ÖZ

Amaç: Bu çalışmamızda mikrodiskektomi yöntemiyle opere ettiğimiz pediatrik yaş grubu lomber disk hernisi (LDH) olgu serisi sunulacaktır.

Gereç ve Yöntem: Temmuz 2013 ve Aralık 2018 tarihleri arasında tek bir cerrah tarafından LDH tanısıyla mikrodiskektomi ile cerrahi tedavi uygulanan dokuz pediatrik hasta postoperatif olarak yaklaşık 1 yıl süreyle takip edilerek postoperatif bel ve bacak ağrıları vizüel analog skala (VAS) skoru ile, 1. yıl da operasyon memnuniyeti MacNab kriterleri ile değerlendirildi.

Bulgular: Çalışmamızda hastalarımızın yaş ortalaması 14,6 idi. Beş hastamız L4-5, dört hastamız L5-S1 seviyesinden opere edildi. Preoperatif VAS ortalaması 8,00±0,70, postoperatif VAS ortalaması 2,00±0,86 idi. VAS puanları arasındaki fark istatistiksel olarak anlamlı idi (p=0,007). Tüm hastalarımız tarafından MacNab skoruna göre iyileşme iyi/mükemmel olarak değerlendirildi.

Sonuç: Çocukluk çağı disk hernileri tedavisinde mikrodiskektomi güvenli ve etkili bir tedavi yöntemidir.

Anahtar Kelimeler: Mikrodiskektomi, çocukluk çağı lomber disk hernisi, MacNab

Address for Correspondence: Doğan Güçlühan Güçlü, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Neurosurgery, İstanbul, Turkey
E-mail: gucluhang@gmail.com ORCID ID: orcid.org/0000-0002-9959-961X

Cite as: Güçlü DG. Pediatric Lumbar Microdiscectomy. Med J Bakirkoy 2022;18:330-335

Received: 24.07.2022
Accepted: 01.08.2022

INTRODUCTION

Lumbar disc herniation (LDH) has been defined as "the displacement of disc material from intervertebral disc range boundaries, regionally or focally". Disc herniations that occur in adulthood often develop because of degeneration. LDH is extremely rare in children and adolescents with healthy lumbar vertebrae and intervertebral disks. The insidance of disc herniation in children and adolescents is approximately 0.1%-0.2%. However 0.5%-6.8% of the patients admitted to the hospital with LDH diagnosis are in the age group of child and adolescent. "Lumbar disc protusion under ten years of age is very rare" this is how it is described in the literature, and the youngest age reported is 13 months (1). Overall, less than 10% of pediatric lower back pain cases are caused by disc herniation, and less than half of these cases require surgery (2,3). Although the pathophysiology of pediatric term LDH is not fully elucidated, risk factors such as trauma, developmental anatomical variants, and genetics play a role in the pathophysiology of pediatric LDH (4-6). In contrast to degenerative discs common in adults, pediatric LDH cases have a lower resorption rate and conservative treatment response due to their higher elasticity and higher liquid content on a nondegenerative background. Open discectomy was widely used until 1980 when the patients unable to perform daily activities due to pain and had progressive neurological deficits that do not benefit from conservative treatment methods. After 80's, minimally invasive surgical methods have been introduced with the advantages of smaller incision sites, less novelization, less bleeding, more limited surgical trauma exposure. The minimally invasive methods used in today's pediatric LDH treatment include microdiscectomy. In this study, we will present you a series of cases with pediatric age LDH operated by microdiscectomy method.

METHODS

In this series of cases: nine pediatric patients under 18 years of age who underwent microdiscectomy operation by a single surgeon, between July 2013 and December 2018. Patients with LDH diagnoses that had been confirmed by physical and neurological examination and magnetic resonance imaging (MRI) examination and patients who did not benefit from at least 2 months of conservative treatment were included. Patients with an acute fracture of the spine due to previous spinal infection or trauma, and the ones with lumbar instability were out of the study. Data were collected both from patient files and electronic medical records. Written consent was obtained from a parent before surgery. The study protocol was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital's Local Ethics Board (decision no: 2021-16-12, date: 16.08.2021).

Before the operation, demographic data including age and gender, trauma at the onset of symptoms, heavy lifting, family history, intense sports activity and whether there was lower back pain-accompanying leg pain in the form of radiculopathy was questioned. During the pre-operation examination, straight leg lift test, lower limb weakness and loss of sensation were recorded and lumbar MRI and in some cases, computed tomography and dynamic radiographs were taken if necessary before the operation to confirm LDH level and side location. Pain was scored according to the visual analog scale (VAS).

The operation records were reviewed for blood loss, complications and postoperative hospitalization. All patients were followed for a period of at least 1 year and postoperative lower back and leg pain were graded with the VAS score. Operation satisfaction was assessed by the MacNab criteria one year after surgery. According to the MacNab criteria: excellent (4): no pain, no work restrictions, good (3): lower back and leg pain, no obstacles to work, medium (2): occasional pain, but unable to continue his job, bad (1): pain, the need for a second surgery (7).

Statistical Analysis

Statistical analysis was performed using IBM SPSS 22.0 for Windows statistical software (IBM Corp., Armonk, NY). Statistical significance was considered as $p<0.05$. Descriptive statistical methods including mean, standard deviation were used. The Wilcoxon test was used to evaluate the difference between pre- and postoperative VAS scores.

Surgical Technique

All patients were operated on in the prone position under general anesthesia after preoperative prophylactic antibiotic therapy. Before the operation, distance control was performed using the C-arm scopy. A 1.5-2.0 cm long skin incision was made in the middle line. The dorsolomber fascia was opened 5 mm laterally from the midline. Paravertebral muscles were removed from medial to lateral by maintaining the facet capsule integrity and taking care not to cross the lateral border of the facet without cutting the adhesion site of the spinous process. The accuracy of the distance was checked again with the C-arm scopy. Caspar microdiscectomy retractor has been inserted. Microscopically, the interlaminar distance is exposed. Partial hemilaminectomy was performed using high-speed drill and kerrison. To reduce postop epidural fibrosis, the nerve root was identified by preserving the league flavum as much

as possible. The size of the disc herniation was observed by gently excluding the nerve root medially by avoiding continuous ecartation. Aggressive discectomy was avoided as reducing disc height could lead to segmental instability, and only the extracted disc fragment was removed. If the annular defect was large, discectomy was performed. If the annular defect was small and the annulus was stable, the normal disc tissue was preserved and fragmentectomy and annuloplasty were performed. The lumbodorsal fascia was closed subcutaneously with 2/0 absorbed suture, with 4/0 absorbed suture under the skin, the skin closed subcutaneously with 4/0 absorbed suture.

RESULTS

Six of our patients were girls (66.6%) and three of them were boys (33.3%) The mean age in our study was 14.6 (+/-1) The youngest was 13 and the eldest was 16 years old. All of our patients were operated with a single distance LDH diagnosis. Three patients were operated from the level of right L4-5, two patients from left L4-5, two patients from right and left L5-S1 with five patients from L4-5 (55%) and four patients operated from L5-S1 (44%) (Figure 1). The average duration of symptoms in our patients was 3.7 months. There were trauma history in four patients (44%), heavy lifting in three patients (33%) and family history in three patients (33%) in lumbar disc hernia etiopathogenesis (Figure 2). All of our patients had leg pain, 5 patients (55%) had leg pain complaints accompanied by back pain. All of our patients tested positive for straight leg lift test. The neurological examination of 4 patients (44%) showed muscle weakness. The mean duration of hospitalization was 1.4 (+/-1.6) days (Table 1).

All of our patients had intraoperative blood loss under 50 mL. Mean preoperative VAS score was 8 (+/-1) mean postoperative VAS score was 2 (+/-1), improvement in preoperative and postoperative VAS score was 6. The mean of preoperatif VAS was 8.00±0.70, while the mean of postoperatif VAS was 2.00±0.86. According to the Wilcoxon test, the significance of the difference between these two averages was calculated as (Z)-2,719 and the difference between VAS preoperative and postoperative scores was statistically significant (p=0.007). According to the MacNab score in all of our patients, recovery was evaluated as good and excellent (Table 2). As a complication, an early superficial infection was observed in a patient and had recovered with oral antibiotic treatment.

DISCUSSION

On average, 10% of children with low back pain have disc herniation, and less than half need surgical intervention as a treatment method (3). The ideal treatment for pediatric LDH is controversial (8,9). Many clinicians recommend conservative treatment as the primary treatment, except for patients with cauda equina syndrome, patients with rapidly developing neurological deficits. Surgery is recommended when conservative treatment fails despite being administered for several months. Some studies have found that LDH in children has a lower success rate of conservative treatment compared to adults (4,10). 25-50% improvement was reported in pediatric LDH patients with no neurological symptoms, who were treated conservatively and monitored for a long time (11). 42% of the pediatric and adolescent group who had been treated by epidural steroid injection with the diagnosis of LDH needed surgical treatment (12). This is explained by the fact that pediatric

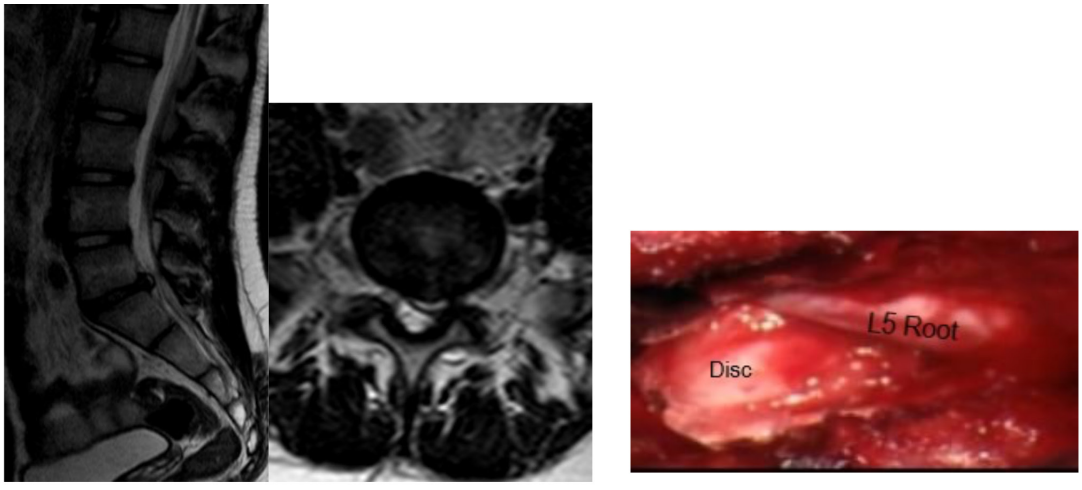

Figure 1. Fifteen years old left L5-S1 HNP; sagital T2, axial T2 and intraoperative imaging
HNP: Herniated nucleus pulposus

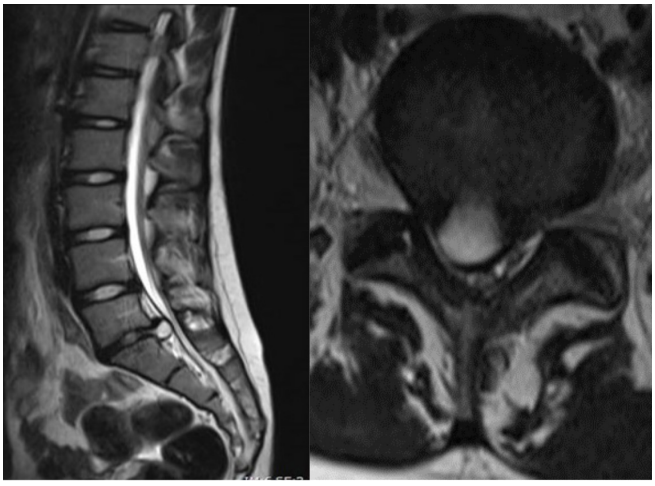

Figure 2. Fourteen years old right L5-S1 traumatic disc herniation

patients are more difficult to adapt to absolute bed rest and are probably accompanied by large annular tear when develop after trauma. Besides, the herniated disc segment is less degenerated compared to adults and the disc is more difficult to absorb due to its hydration and gelatin structure (13). In 1945, Wahren (14) published the case of a 12-year-old gymnast girl who did not benefit from one month of conservative treatment as the first pediatric disc hernia to be surgically operated with the diagnosis of right L5-S1.

The mean age in our study was 14.6 (+/-1) The youngest was 13 years old and the oldest was 16 years old. Similar to our findings, LDH was observed in 97.5% between 13 and 18 and 2.5% under 12 (15). LDH under twelve years of age had defined very rarely in the literature (16). No cases operated under 12 years in our series. During the last 30 years, only 8 surgical cases under 10 years of age have been published (17).

In our study, 6 of our patients were female (66.6%) and 3 (33.3%) were male. Similar to our results, McAvoy et al. (18) reported that 111 of 199 pediatric patients (55.8%) who underwent microdiscectomy were reported as girls. Another series of pediatric cases that underwent lumbar discectomy reported 58% of the patients as girls (19). While girls undergo puberty and hence, the growth rate peaks between 11 and 15 years old, this process is between 13 and 17 years old for boys. Bone and ligaments mature earlier in women. Here, it has been emphasized that LDH is more common in female patients due to early onset of degeneration than in males by completing maturation at an early age. In our study, LDH etiopathogenesis had trauma in four patients (44%), heavy lifting in three patients (33%) and family history in three patients (33%). The rate of trauma history in patients with childhood LDH varies between 8% and 82% in the literature (20). In some studies, it has been stated that trauma is not the main factor, but it increases the current disease and makes it symptomatic (21,22). 13%-57% of pediatric cases reported that there was also LDH in their first degree family members. In a study by Theodore et al. (23), 80% of childhood disc hernias had mutations in the structure that encode collagen.

In our study, five patients were operated from L4-5 (55%) to four patients from L5-S1 (44%). A study by Raghu et al. (17) reported that LDH in children and adolescents treated with surgery was frequent (52%) at levels L4-5 and (41%) L5-S1 (19). In-wide sample follow-up studies, L4-5 levels (60.3%), L5-S1 (42.7%) and L3-4 (9.5%) were indicated in order of frequency (20). The most commonly affected distance in the adult age group has been reported as L5-S1 (24).

In our study, while all of our patients had leg pain, five patients (55%) complained of lower back pain. Ozgen et al. (25) reported that 88% of patients had low back pain,

Table 1. Socio-demograpic and clinical variables

Age	Gender	Level	Side	Cause	FH	SLLT	Motor deficite	Pain locazition	Pain duration	HS/day
13	F	L4-5	R	TH	-	10	-	Leg	6 m	2
16	F	L5-S1	L	HL	-	20	-	Leg + Back	3 m	2
15	M	L5-S1	R	HL	-	45	PF 4/5	Leg	3 m	1
14	F	L4-5	L	TH	-	30	EHL 4/5	Leg + Back	2 m	2
16	F	L4-5	L	HL	+	30	EHL 4/5	Leg	5 m	1
14	F	L5-S1	R	-	+	45	-	Leg	6 m	1
15	M	L4-5	R	-	+	30	-	Leg + Back	4 m	1
15	F	L5-S1	L	TH	-	30	-	Leg + Back	3 m	1
14	M	L4-5	R	TH	-	45	DF4/5	Leg + Back	2 m	2

F:Female, M: Male, R: Right, L: Left, HL: Heavy lifting, TH: Trauma history, FH: Family history, m: Month, SLLT: Straight leg lift test, HS: Hospital stay

Table 2. Preoperative and postoperative VAS and MacNab scores

VAS Preop	VAS Postop	MacNab
9	2	4
8	2	3
8	3	3
8	2	3
8	3	3
7	1	4
8	1	4
9	3	3
7	1	4

VAS: Visual analog scale

whereas 35% had sciatic pain spread. McAvoy et al. (18) reported that 98.0% of cases were referred by radicular pain with 66.3% lower back pain.

In our study, muscle weakness was detected in 4 patients (44%) who tested positive for straight leg lift test during neurological examination. In patients with low back pain and radiculopathy, the sensibility of this test was found to be higher than expected in the pediatric age group (26). In the adult age group, it has been reported that the sciatic nerve, which is less mobilized due to peridural adhesion, is important in the formation of pain in the straight leg lift test (27). McAvoy et al. (18) evaluated the straight leg lift test as 98.9% positive in their study in the Pediatric Group. Older patients have less mobile sciatic nerves, related to peridural fibrotic adhesions, which are thought to be important for pain generation on straight leg raising (18).

About 90% of symptomatic disc herniation occurs at vertebra levels L4-L5 and L5-S1. Disc herniation in L4-L5 most commonly affects the L5 nerve root. The weakness of the extensor hallusis longus muscle can be seen with L5 nerve root compression. Sensory abnormalities can be seen in the dorsal part of the foot. There was no deep tendon reflex associated with the L5 nerve root. The S1 nerve root is most commonly affected by disc herniation in L5-S1. S1 nerve root compression can cause plantar flexion and eversion of the ankle to weaken. The Achilles tendon reflex must be tested because S1 is an indicator of nerve root function. Cahill et al. (15) found lower limb motor weakness in 26% of patients, decreased sensation in 41%, and deep tendon reflex loss in 22%. In the study by McAvoy et al. (18), sensory changes were reported as 32%, lower limb motor weakness, and loss of deep tendon reflexes as 19.0% and 18.5%, respectively. Raghu et al. (17) had determined motor deficits loss to be 43%.

In our study mean preoperative VAS score was 8 (+/-1) mean postoperative VAS score was 2 (+/-1). Mean improvement in VAS score in the postoperative first year was found to be. All of our patients in post-operative first year rated their improvement as good/excellent. The recovery and long-term prognosis in pediatric patients is much better than in adults (27). Çelik et al. (28) compared 32 pediatric and adult patients who underwent lumbar microdiscectomy. It has been reported that a significant decrease in pain in the pediatric group in the short- and long term follow-up furthermore, reherniation and postoperative epidural fibrotic changes were reported to be higher in the adult group (28). In a Swedish study, it was shown that leg and back pain was significantly reduced in the pediatric group after surgery compared with adults at 1 or 2 years of follow-up (average =1.7 years) (29). In 2019, a study by McAvoy et al. (18) also reported surgical satisfaction as good and excellent in 90% of 199 pediatric cases.

The mean duration of hospitalization in our study was 1.4 (+/-1.6) days. Intraoperative blood loss in all our patients was under 50 mL. An early superficial infection in a patient who had been treated with oral antibiotics. Perioperative (1.0%), and postoperative (2.6%) complications with microdiscectomy applied in the pediatric age group are rare in the literature. Studies show (17,26) low rates of deep and superficial infection in pediatric degenerative spine surgery (<1%) and minimally invasive techniques are associated with lower infection rates than open surgery (30).

CONCLUSION

Childhood disc hernias are a fairly rare clinical condition. If there is a significant and/or progressive neurological deficit and no response with conservative treatment, microdiscectomy is a safe and effective treatment.

ETHICS

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital's Local Ethics Board (decision no: 2021-16-12, date: 16.08.2021).

Informed Consent: Written consent was obtained from a parent before surgery.

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

REFERENCES

1. MacGee EE. Protruded lumbar disc in a 9-year-old boy. J Pediatr 1968;73:418-9.
2. Carey TS, Garrett J, Jackman A, McLaughlin C, Fryer J, Smucker DR. The outcomes and costs of care for acute low back pain among patients seen by primary care practitioners, chiropractors, and orthopedic surgeons. The North Carolina Back Pain Project. N Engl J Med 1995;333:913-7.
3. Durham SR, Sun PP, Sutton LN. Surgically treated lumbar disc disease in the pediatric population: an outcome study. J Neurosurg 2000;92(1 Suppl):1-6.
4. Kurihara A, Kataoka O. Lumbar disc herniation in children and adolescents. A review of 70 operated cases and their minimum 5-year follow-up studies. Spine (Phila Pa 1976) 1980;5:443-51.
5. DeLuca PF, Mason DE, Weiand R, Howard R, Bassett GS. Excision of herniated nucleus pulposus in children and adolescents. J Pediatr Orthop 1994;14:318-22.
6. Bradford DS, Garcia A. Herniations of the lumbar intervertebral disk in children and adolescents. A review of 30 surgically treated cases. JAMA 1969;210:2045-51.
7. Macnab I. Negative disc exploration. An analysis of the causes of nerve-root involvement in sixty-eight patients. J Bone Joint Surg Am 1971;53:91-903.
8. Dang L, Liu Z. A review of current treatment for lumbar disc herniation in children and adolescents. Eur Spine J 2010;19:205-14.
9. Dang L, Chen Z, Liu X, Guo Z, Qi Q, Li W, et al. Lumbar Disk Herniation in Children and Adolescents: The Significance of Configurations of the Lumbar Spine. Neurosurgery 2015;77:954-9.
10. Kurth AA, Rau S, Wang C, Schmitt E. Treatment of lumbar disc herniation in the second decade of life. Eur Spine J 1996;5:220-4.
11. Zamani MH, MacEwen GD. Herniation of the lumbar disc in children and adolescents. J Pediatr Orthop 1982;2:528-33.
12. Kurgansky KE, Rodriguez ST, Kralj MS, Mooney JJ, Dinakar P, d'Hemecourt PA, et al. Epidural Steroid Injections for Radiculopathy and/or Back Pain in Children and Adolescents: A Retrospective Cohort Study With a Prospective Follow-Up. Reg Anesth Pain Med 2016;41:86-92.
13. Dang L, Liu Z. A review of current treatment for lumbar disc herniation in children and adolescents. Eur Spine J 2010;19:205-14.
14. WAHREN H. Herniated nucleus pulposus in a child of twelve years. Acta Orthop Scand 1945;16:40-2.
15. Cahill KS, Dunn I, Gunnarsson T, Proctor MR. Lumbar microdiscectomy in pediatric patients: a large single-institution series. J Neurosurg Spine 2010;12:165-70.
16. Revuelta R, De Juambelz PP, Fernandez B, Flores JA. Lumbar disc herniation in a 27-month-old child. Case report. J Neurosurg 2000;92(1 Suppl):98-100.
17. Raghu ALB, Wiggins A, Kandasamy J. Surgical management of lumbar disc herniation in children and adolescents. Clin Neurol Neurosurg 2019;185:105486.
18. McAvoy M, McCrea HJ, Chavakula V, Choi H, Bi WL, Mekary RA, et al. Long-term outcomes of lumbar microdiscectomy in the pediatric population: a large single-institution case series. J Neurosurg Pediatr 2019:1-9.
19. Strömqvist F, Strömqvist B, Jönsson B, Gerdhem P, Karlsson MK. Lumbar disc herniation surgery in children: outcome and gender differences. Eur Spine J 2016;25:657-63.
20. Karademir M, Eser O, Karavelioglu E. Adolescent lumbar disc herniation: Impact, diagnosis, and treatment. J Back Musculoskelet Rehabil 2017;30:347-52.
21. Parisini P, Di Silvestre M, Greggi T, Miglietta A, Paderni S. Lumbar disc excision in children and adolescents. Spine (Phila Pa 1976) 2001;26:1997-2000.
22. Kumar R, Kumar V, Das NK, Behari S, Mahapatra AK. Adolescent lumbar disc disease: findings and outcome. Childs Nerv Syst 2007;23:1295-9.
23. Theodore N, Ahmed AK, Fulton T, Mousses S, Yoo C, Goodwin CR, et al. Genetic Predisposition to Symptomatic Lumbar Disk Herniation in Pediatric and Young Adult Patients. Spine (Phila Pa 1976) 2019;44:E640-9.
24. Gulati S, Madsbu MA, Solberg TK, Sørlie A, Giannadakis C, Skram MK, et al. Lumbar microdiscectomy for sciatica in adolescents: a multicentre observational registry-based study. Acta Neurochir (Wien) 2017;159:509-16.
25. Ozgen S, Konya D, Toktas OZ, Dagcinar A, Ozek MM. Lumbar disc herniation in adolescence. Pediatr Neurosurg 2007;43:77-81.
26. Tabesh H, Tabesh A, Fakharian E, Fazel M, Abrishamkar S. The effect of age on result of straight leg raising test in patients suffering lumbar disc herniation and sciatica. J Res Med Sci 2015;20:150-3.
27. Slotkin JR, Mislow JM, Day AL, Proctor MR. Pediatric disk disease. Neurosurg Clin N Am 2007;18:659-67.
28. Çelik S, Göksu K, Çelik SE, Emir CB. Benign neurological recovery with low recurrence and low peridural fibrosis rate in pediatric disc herniations after lumbar microdiscectomy. Pediatr Neurosurg 2011;47:417-22.
29. Lagerbäck T, Elkan P, Möller H, Grauers A, Diarbakerli E, Gerdhem P. An observational study on the outcome after surgery for lumbar disc herniation in adolescents compared with adults based on the Swedish Spine Register. Spine J 2015;15:1241-7.
30. Smith JS, Shaffrey CI, Sansur CA, Berven SH, Fu KM, Broadstone PA, et al. Rates of infection after spine surgery based on 108,419 procedures: a report from the Scoliosis Research Society Morbidity and Mortality Committee. Spine (Phila Pa 1976) 2011;36:556-63.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:336-340
DOI: 10.4274/BMJ.galenos.2022.2022.5-8

Research

Does Growth Hormone Therapy Enlarge Pituitary Adenomas?

Büyüme Hormonu Tedavisi Hipofiz Adenomlarını Büyütür mü?

Eda Çelebi Bitkin[1], Cengiz Kara[2], Serap Karaman[3], Murat Başaranoğlu[3], Adem Yokuş[4], Oğuz Tuncer[3]

[1]Van Yüzüncü Yıl University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, Van, Turkey
[2]İstinye University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, İstanbul, Turkey
[3]Van Yüzüncü Yıl University Faculty of Medicine, Department of Pediatrics, Van, Turkey
[4]Van Yüzüncü Yıl University Faculty of Medicine, Department of Radiology, Van, Turkey

ABSTRACT

Objective: Pituitary adenomas are detected incidentally in some cases of childhood growth hormone deficiency. Growth hormones may affect tumor growth. This study analyzed the reliability of growth hormone therapy in patients with non-functioning pituitary adenomas.

Methods: The study group included 16 hypopituitary patients with incidentally detected non-functioning pituitary adenoma and treated with recombinant growth hormone. Age- and sex-matched 16 healthy children with incidental pituitary adenoma detected during investigation of chronic headache were selected as the control group. The data of the two groups were retrospectively reviewed and compared regarding the change in adenoma size over time.

Results: Changes in adenoma size in the patient and control groups were -0.1 (-0.8-0.3) mm and -0.1 (-0.5-0.3) mm, respectively (p=0.664). Adenoma size growth was detected in 3 patients in the patient group and 5 patients in the control group (p=0.685).

Conclusion: Our data suggest that recombinant growth hormone therapy does not produce pituitary adenomas, and thus its use is safe in growth hormone deficient children with incidentally detected non-functioning pituitary adenomas.

Keywords: Growth hormone therapy, pituitary adenoma, pediatric endocrinology

ÖZ

Amaç: Hipofiz adenomları çocukluk çağı büyüme hormonu eksikliği olan bazı olgularında tesadüfen saptanır. Büyüme hormonu tümör büyümesini etkileyebilir. Bu çalışma, non-fonksiyone hipofiz adenomu olan hastalarda büyüme hormonu tedavisinin güvenilirliğini analiz etmektedir.

Gereç ve Yöntem: Çalışma grubuna, insidental olarak saptanan ve non-fonksiyone hipofiz adenomu olan ve rekombinant büyüme hormonu ile tedavi edilen 16 hipopitüitarizmli hasta dahil edildi. Kronik baş ağrısı incelemesi sırasında insidental olarak hipofiz adenomu saptanan yaş ve cinsiyet açısından uyumlu 16 sağlıklı çocuk kontrol grubu olarak seçildi. İki grubun verileri geriye dönük olarak incelendi ve adenom boyutunun zaman içindeki değişimi karşılaştırıldı.

Bulgular: Hasta ve kontrol gruplarında adenom boyutundaki değişiklikler sırasıyla -0,1 (-0,8-0,3) mm ve -0,1 (-0,5-0,3) mm idi (p=0,664). Hasta grubunda 3, kontrol grubunda 5 hastada adenom boyutunda büyüme saptandı (p=0,685).

Sonuç: Verilerimiz rekombinant büyüme hormonu tedavisinin hipofiz adenomlarını büyütmediğini ve bu nedenle insidental olarak saptanan non-fonksiyone hipofiz adenomu olan büyüme hormonu eksikliği olan çocuklarda kullanımının güvenli olduğunu göstermektedir.

Anahtar Kelimeler: Büyüme hormonu tedavisi, hipofiz adenomu, pediatrik endokrinoloji

Address for Correspondence: Eda Çelebi Bitkin, Van Yüzüncü Yıl University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, Van, Turkey
Phone: +90 530 764 24 06 E-mail: edacelebitkin@gmail.com ORCID ID: orcid.org/0000-0002-6586-7305

Cite as: Çelebi Bitkin E, Kara C, Karaman S, Başaranoğlu M, Yokuş A, Tuncer O. Does Growth Hormone Therapy Enlarge Pituitary Adenomas?. Med J Bakirkoy 2022;18:336-340

Received: 18.05.2022
Accepted: 13.08.2022

INTRODUCTION

Recombinant growth hormone (rGH) therapy is used for treating short stature resulting from GH deficiency or other diseases during childhood (1). The causes of GH deficiency include space-occupying lesions and structural defects of the pituitary, and so pituitary magnetic resonance imaging (MRI) is used as a routine part of etiological evaluation before treatment (2). Pituitary adenomas are incidentally detected at a rate of 0.5%-20.3% in cases of childhood GH deficiency (3,4). GH is a mitogenic agent, that increases the levels of insulin-like growth factor-1 (IGF-1). This, in turn, raises concerns about its potential to be involved in tumor development and tumor growth (5). There are few data on the effect of rGH treatment on pituitary non-functioning adenoma (NFA) in children (4). This study examines the effect of rGH therapy on adenoma sizes in children diagnosed with GH deficiency.

METHODS

We retrospectively reviewed the file records of 87 patients who presented to the pediatric endocrinology outpatient clinic between 2011 and 2021 due to short stature, and that were diagnosed with GH deficiency. NFA was detected in the pituitary MRI of 16 patients. Age- and sex-matched 16 healthy children with incidental pituitary adenoma detected during investigation of chronic headache were selected as the control group.

rGH treatment was given to the patient group at a dose of 29.8 (26.3-33.5) µg/kg/day. IGF-1 levels were between +1 standard deviation score (SDS) and + 2 SDS during the treatment periods. Diagnoses of GH deficiency were established on the basis of short stature (height SDS <-2), growth rate SDS <-1 and a low level of IGF-1 for the child's age; and a low response (peak GH <10 ng/mL) to two GH provocation tests (L-dopa and clonidine). All patients underwent a pituitary MRI (Magnetom Amira, Siemens Medical Systems, Forcheim, Germany) before starting GH therapy. The pituitary MRI examination involved the measurement of the anteroposterior long diameter on the sagittal T1-weighted sequence (Figure 1). In the patient group and control group, all patients had microadenoma (<10 mm). For all cases, other anterior pituitary functions were evaluated by measuring the levels of IGF-1, IGF-binding protein 3, prolactin, adrenocorticotropic hormone (ACTH), cortisol, free thyroxine (fT4) and thyroid-stimulating hormone (TSH). The control pituitary MR images of the patient group and control group were reviewed, and changes in the size of the pituitary adenomas were recorded. The adenoma sizes in all patents were measured and compared before, and during the final treatment, by the same experienced radiologist. Approval for this study was obtained from the Van Yüzüncü Yıl University Clinical Research Ethics Committee (decision no: 2019/17-13, date: 06.12.2019).

Statistical Analysis

Statistical analyses were performed using the SPSS software version 15. Descriptive analyses were presented using medians and interquartile range due to the small number of cases. The Mann-Whitney U test was used to compare adenoma sizes at baseline and follow-up between the patient and control groups. Fisher's Exact test was conducted to compare the ordinal variables between groups. Also, the Wilcoxon test was used to compare the change in adenoma size between baseline and follow-up in each one group. A p-value of less than 0.05 was considered a statistically significant result.

RESULTS

NFA was detected in 16 (18.3%) of 87 patients diagnosed with GH deficiency. In the patient group, 5 patients had multiple pituitary hormone deficiency (3 patients had GH-TSH; 1, GH-TSH-gonadotropin; and 1, panhypopituitarism). The remaining 11 patients had isolated GH deficiency. In the patient group with multiple pituitary hormone deficiency, screening of *PROP1, POU1F1, HESX1, LHX3, LHX4, and OTX2* genes did not show any pathogenic variation. As shown in Table 1, there were no statistically significant differences between the patient and control groups regarding age, gender, location of pituitary adenoma, follow-up duration, and adenoma sizes at baseline and follow-up. The median treatment duration was 3.1 (1.4-5.0) years in the patient group. The median durations of interval between first and last MRI were 1.2 (0.8-3.9) and 1.6 (1.0-2.3) years in patient and control groups, respectively (p=0.649). Changes in adenoma size in patient and control groups were -0.1 (-0.8-0.3) mm and -0.1 (-0.5-0.3) mm, respectively (p=0.664). Comparisons of adenoma sizes between baseline and follow-up in each one group showed no statistically significant difference. Adenoma size growth was detected in 3 patients (19%) in the patient group and 5 patients (31%) in the control group, but this difference was not statistically significant (p=0.685).

DISCUSSION

Replacement therapy is commonly used in children with GH deficiency, although concerns have been raised about the safety of GHs due to their potentially stimulating effect on tumor growth (6).

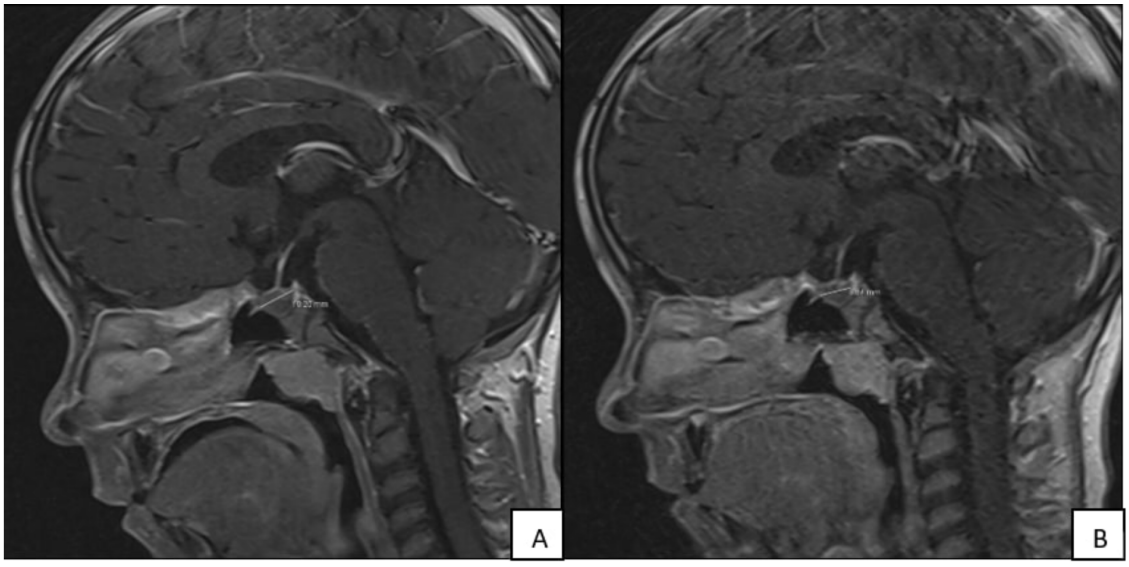

Figure 1. Pituitary MRI anterior-posterior image. A: before growth hormone therapy (10.2 mm), B: 1 year after growth hormone therapy (8.6 mm)
MRI: Magnetic resonance imaging

Table 1. Demographic data, and pituitary adenoma sizes at baseline and during follow-up

	Patient group (n=16)	Control group (n=16)	p-value
Age (years)	13.6 (10.7-14.5)	13.0 (12.2-15.4)	0.564
Gender (F/M)	6/10	7/9	0.719
Location of pituitary adenoma (C/R/L)	10/3/3	11/2/3	0.884
Duration of GH treatment (years)	3.1 (1.4-5.0)	-	-
Interval between first and last MRI (years)	1.2 (0.8-3.9)	1.6 (1.0-2.3)	0.649
Adenoma size at baseline (mm)	5.0 (3.5-5.1)*	4.3 (2.8-5.6)*	0.445
Adenoma size at follow-up (mm)	4.9 (3.5-5.6)*	4.3 (2.4-5.3)*	0.564
Change in adenoma size over time (mm)	-0.1 (-0.8-0.3)	-0.1 (-0.5-0.3)	0.664
Ratio of growing adenoma in size (%)	19	31	0.685

Data were presented using medians and interquartile range. *Comparisons of adenoma sizes between baseline and follow-up showed p-values of 0.22 and 0.795 in patient and control groups, respectively.

F: Female, M: Male, C: Central, R: Right, L: Left, MRI: Magnetic resonance imaging, GH: Growth hormone

NFAs can be detected on pituitary MRIs performed before GH therapy. Therefore, the possibility of GH therapy to enlarge concomitant pituitary adenoma is also of concern. Our study showed that GH therapy did not exert such an enlargement effect on concomitant pituitary adenoma size.

There have been very few studies addressing the effects of the GH treatment on adenoma size in childhood (4). In the study by Derrick et al. (4), the lesions did not grow after treatment in children with pituitary microadenoma who were treated with rGH and most of them were not observed on repeat imaging. In that study, the patient group was not compared with a control group that did not receive GH treatment. Additionally, it was reported that 17% of the patients did not start treatment because of the detection of NFA (4). Nonfunctional adenomas have potential disadvantages such as influencing the decision to initiate rGH treatment and patient/parent anxiety. Our study makes an additional contribution to the limited studies conducted on the effects of rGH treatment on NFA in children, and to the existing knowledge because it is a case-control study.

Basic research has shown that GH and IGF-1 are likely to play a role in tumor development and growth through cell proliferation and apoptosis regulation (6). Because of these effects of GHs, several studies have been conducted, but mostly with adults, regarding its reliability. The adult studies evaluating the effect of GH therapy, especially in NFA patients, were unable to establish any tumor growth or increased frequency of recurrence (6-9).

Buchfelder et al. (8) conducted a retrospective case control study to investigate the safety of GH in patients with NFA who were treated surgically. The authors identified no significant increase in tumor growth between the patients treated with GH and a control group who underwent no such treatment (8). Arnold et al. (7) evaluated the effect of GH therapy on tumor recurrence in 130 NFA patients who were treated only surgically and followed up at a single center. Tumor progression was noted in 35% of 23 patients undergoing GH therapy, and 36% of the 107 patients receiving no such therapy. Accordingly, the authors concluded that GH therapy did not cause progression (7). A previous meta-analysis of adults reported 10%-spontaneous growth of pituitary microadenomas (10). Previous adult studies investigating the effect of GH therapy on NFAs found them to contain more confusing factors (growth and pressure effects of NFA in advanced age and the development of other hormone deficiencies, possibility of surgical operation and radiotherapy due to pressure effects, etc.) compared to the pediatric patient group. We believe that the said study would provide more objective information on the pediatric patient group. The data in this study support the claim that GH therapy does not enlarge pituitary adenomas.

A previous meta-analysis used epidemiological, postmortem and radiological study data to estimate the prevalence of pituitary adenomas and reported an estimated prevalence of pituitary adenoma of 16.7% for the general population (11). A study of adults reported prevalence of microadenomas varying between 10% and 31.1% (10). Hirsch et al. (12), in turn, found microadenomas in 29% of children. A study by Derrick et al. (4) identified microadenomas in 20.3% of 261 patients with detected GH deficiency. A review of the Pfizer International Growth Database (KIGS database) examined 15,000 patients and identified pituitary microadenoma in 0.5% of the patients with GH deficiency (3). In this study, pituitary microadenomas were found in 16 (18.3%) of the 87 GH deficiency patients being followed up by our clinic. Our study presents new data on the incidence of microadenomas on pituitary MRIs of children with GH deficiency, and supports the study by Derrick et al. (4), which reported a relatively high rate. There is no clear difference in the prevalence of pituitary adenoma between the general population and GH deficiency patients. Nevertheless, the necessity to initiate treatment in patients with GH deficiency makes the pituitary adenoma more of a concern than it is for the general population (4). Therefore, in our study, we assessed whether such a concern is justified and observed that rGH treatment did not enlarge the size of pituitary adenomas and can be safely used in children with hypopituitarism and NFA.

Typical findings of microadenoma on a pituitary MRI include abnormal signal intensity on unenhanced images and delayed contrast enhancement after contrast administration (12). When a microadenoma is detected, the clinician must determine whether or not the tumor is functional. Functional microadenomas secrete extreme number of such pituitary hormones as, mostly, prolactin, and less frequently ACTH or GH (13,14). None of the children in the patient and control groups had any clinical signs of hormonal hyperfunction, and laboratory data showed that there was no hypersecretion of prolactin or ACTH. That said, NFAs may, theoretically, lead to hormone deficiencies through their mass effect on the adjacent pituitary tissue (13,14). Microadenomas are usually confined to sella turcica, and therefore, do not create a mass effect that can be detected through visual changes or other symptoms. Derrick et al. (4) demonstrated that pituitary microadenomas are common in cases of childhood GH deficiency; however, they are usually not the cause of the GH deficiency in childhood. In this study, most adenomas being microadenomas (<1 cm), their localization (not pressuring the stalk) and the lack of any identifiable visual changes gives the impression that it is not a prominent etiological factor.

The limitations of this study relate to its retrospective and the small number of cases.

CONCLUSION

As a result, this study identified non-functioning pituitary adenoma in 18.3% of children with GH deficiency. No significant difference was established in existing adenoma sizes after GH therapy. When the changes in adenoma size in both groups were compared, there was no significant difference. These data support the suggestion that GH therapy is safe in children with detected NFA, although there is a need for prospective randomized studies involving a larger number of cases.

ETHICS

Ethics Committee Approval: Approval for this study was obtained from the Van Yüzüncü Yıl University Clinical Research Ethics Committee (decision no: 2019/17-13, date: 06.12.2019).

Informed Consent: Retrospective study.

Authorship Contributions

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

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

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

REFERENCES

1. Halas JG, Grimberg A. Dilemmas of growth hormone treatment for GH deficiency and idiopathic short stature: defining, distinguishing, and deciding. Minerva Pediatr 2020;72:206-25.
2. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab 2000;85:3990-3.
3. Maghnie M, Lindberg A, Koltowska-Häggström M, Ranke MB. Magnetic resonance imaging of CNS in 15,043 children with GH deficiency in KIGS (Pfizer International Growth Database). Eur J Endocrinol 2013;168:211-7.
4. Derrick KM, Gomes WA, Gensure RC. Incidence and Outcomes of Pituitary Microadenomas in Children with Short Stature/Growth Hormone Deficiency. Horm Res Paediatr 2018;90:151-60.
5. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004;363:1346-53.
6. van Varsseveld NC, van Bunderen CC, Franken AA, Koppeschaar HP, van der Lely AJ, Drent ML. Tumor Recurrence or Regrowth in Adults With Nonfunctioning Pituitary Adenomas Using GH Replacement Therapy. J Clin Endocrinol Metab 2015;100:3132-9.
7. Arnold JR, Arnold DF, Marland A, Karavitaki N, Wass JA. GH replacement in patients with non-functioning pituitary adenoma (NFA) treated solely by surgery is not associated with increased risk of tumour recurrence. Clin Endocrinol (Oxf) 2009;70:435-8.
8. Buchfelder M, Kann PH, Wüster C, Tuschy U, Saller B, Brabant G, et al. Influence of GH substitution therapy in deficient adults on the recurrence rate of hormonally inactive pituitary adenomas: a case control study. Eur J Endocrinol 2007;157:149-56.
9. Olsson DS, Buchfelder M, Schlaffer S, Bengtsson BA, Jakobsson KE, Johannsson G, et al. Comparing progression of non-functioning pituitary adenomas in hypopituitarism patients with and without long-term GH replacement therapy. Eur J Endocrinol 2009;161:663-9.
10. Molitch ME. Nonfunctioning pituitary tumors. Handb Clin Neurol 2014;124:167-84.
11. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas: a systematic review. Cancer 2004;101:613-9.
12. Hirsch W, Zumkeller W, Teichler H, Jassoy A, Schlüter A, Langer T. Microadenomas of the pituitary gland in children with and without hypophyseal dysfunction in magnetic resonance imaging. J Pediatr Endocrinol Metab 2002;15:157-62.
13. Cannavò S, Venturino M, Curtò L, De Menis E, D'Arrigo C, Tita P, et al. Clinical presentation and outcome of pituitary adenomas in teenagers. Clin Endocrinol (Oxf) 2003;58:519-27.
14. Buurman H, Saeger W. Subclinical adenomas in postmortem pituitaries: classification and correlations to clinical data. Eur J Endocrinol 2006;154:753-8.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:341-347
DOI: 10.4274/BMJ.galenos.2022.2022.6-10

Research

A Prospective Analysis of the Association Between Sexual Dysfunction and Idiopathic Sensorineural Hearing Loss in Men

Erkeklerde Cinsel İşlev Bozukluğu ile İdiyopatik Sensörinöral İşitme Kaybı Arasındaki İlişkinin Prospektif Bir Analizi

Doğan Çakan[1], Semih Uşaklıoğlu[2]

[1]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Otorhinolaryngology, İstanbul, Turkey
[2]University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, Clinic of Otorhinolaryngology, İstanbul, Turkey

ABSTRACT

Objective: The aim was to investigate the relationship between idiopathic sudden sensorineural hearing loss (ISSHL) and male sexual dysfunction (SD).

Methods: Nineteen ISSHL patients were included in the patient group. The control group consisted of nineteen healthy subjects. The pure tone mean (PTM) was determined by averaging the hearing thresholds (250, 500, 1,000, 2,000, 4,000, and 8,000 Hz). Male SD was assessed using the International Index of Erectile Function (IIEF)-5 survey. IIEF-5 items are grouped as the first 4 (IIEF-$5_{Q1\text{-}Q4}$) and the final item (IIEF-5_{Q5}). Intratympanic steroid treatments were administered on the 1st, 3rd, 5th, 7th, 14th, and 30th days of ISSHL diagnosis. Twenty sessions of hyperbaric oxygen therapy were applied to the patients starting from the first day of diagnosis. On the 180th day of the study, patients with hearing gain of less than 15 dB and a PTM value of less than 75 dB were considered treatment failures. The questionnaires of the patients who were successful with the treatment were repeated. The obtained data were analyzed statistically.

Results: Pre-treatment IIEF-5 and IIEF-$5_{Q1\text{-}Q4}$ scores were significantly lower than those of the control group ($p<0.05$). Post-treatment IIEF-5 and IIEF-$5_{Q1\text{-}Q4}$ scores were significantly higher than the pre-treatment scores ($p<0.05$). Erectile dysfunction (ED) suspicion in the IIEF-5 questionnaire results was significantly higher in ISSHL patients ($p=0.002$). For ISSHL patients, ED suspicion was significantly lower in the post-treatment period compared in the pre-treatment period ($p=0.002$).

Conclusion: ISSHL may be accepted as a risk factor for SD. ISSHL can affect sexual life and therefore quality of life.

Keywords: Erectile dysfunction, hearing loss, sensorineural, questionnaires, recovery of function, male, sexual dysfunction, physiological

ÖZ

Amaç: Bu çalışmanın amacı idiyopatik ani sensörinöral işitme kaybı (ISSHL) ile erkek cinsel işlev bozukluğu (SD) arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Çalışmanın hasta grubuna 19 ISSHL hastası dahil edildi. Kontrol grubu 19 sağlıklı bireyden oluşturuldu. Saf ton ortalaması (PTM), işitme eşiklerinin (250, 500, 1.000, 2.000, 4.000 ve 8.000 Hz) ortalaması alınarak belirlendi. Erkek SD, Uluslararası Erektil Fonksiyon İndeksi (IIEF)-5 anketi kullanılarak değerlendirildi. IIEF-5 maddeleri ilk 4 (IIEF-$5_{Q1\text{-}Q4}$) ve son madde (IIEF-5_{Q5}) olacak şekilde gruplandırıldı. ISSHL tanısının 1., 3., 5., 7., 14. ve 30. günlerinde intratimpanik steroid tedavisi uygulandı. Hastalara tanının ilk gününden itibaren 20 seans hiperbarik oksijen tedavisi uygulandı. Çalışmanın 180. gününde işitme kazancı 15 dB'nin altında ve PTM değeri 75 dB'nin altında olan hastalar tedavi başarısızlığı olarak kabul edildi. Tedavisi başarılı olan hastaların anketleri tekrarlandı. Elde edilen veriler istatistiksel olarak analiz edildi.

Bulgular: Tedavi öncesi IIEF-5 ve IIEF-$5_{Q1\text{-}Q4}$ puanları kontrol grubuna göre anlamlı derecede düşüktü ($p<0,05$). Tedavi sonrası IIEF-5 ve IIEF-$5_{Q1\text{-}Q4}$ puanları tedavi öncesine göre anlamlı derecede yüksekti ($p<0,05$). IIEF-5 anket sonuçlarına göre erektil disfonksiyon (ED) şüphesi olan denek sayısı ISSHL hastalarında anlamlı olacak şekilde daha yüksekti ($p=0,002$). ED şüphesi olan ISSHL hastası sayısı tedavi öncesi döneme göre tedavi sonrası dönemde anlamlı olacak şekilde daha düşüktü ($p=0,002$).

Address for Correspondence: Doğan Çakan, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Otorhinolaryngology, İstanbul, Turkey
Phone: +90 554 963 91 29 E-mail: drdgnckn@gmail.com ORCID ID: orcid.org/0000-0002-6283-2916

Cite as: Çakan D, Uşaklıoğlu S. A Prospective Analysis of the Association Between Sexual Dysfunction and Idiopathic Sensorineural Hearing Loss in Men. Med J Bakirkoy 2022;18:341-347

Received: 21.06.2022
Accepted: 31.08.2022

Sonuç: ISSHL, SD için bir risk faktörü olarak kabul edilebilir. ISSHL cinsel yaşamı ve dolayısıyla yaşam kalitesini etkileyebilir.

Anahtar Kelimeler: Erektil disfonksiyon, işitme kaybı, sensörinöral, anket çalışması, fonksiyonun geri kazanılması, erkek, cinsel işlev bozukluğu, fizyolojik

INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISSHL) is defined as a rapid-onset acute hearing loss of at least 30 decibels at three consecutive frequencies occurring over a 3-day (72 h) period, with no identifiable cause (1,2). The incidence in different studies has been determined as 11-77 per 100,000 people per year (3). Although there is no definite known cause of this disease, which can cause hearing loss of varying severity, ranging from mild to total loss, viral infections, vascular disorders, immune-mediated reactions, autonomic nervous system-related diseases, and cochlear membrane rupture are included in the pathogenesis of ISSHL (1-4). ISSHL is associated with different system diseases and affects the quality of life (QoL) of patients (4).

Male sexuality, a dynamic and sophisticated process, is an important part of the QoL (5,6). Male sexual dysfunction does not describe a single condition. It is a disorder that occurs in at least one of the basic male sexual functions such as desire, male sexual arousal, erection, orgasm, and ejaculation (5). Erectile dysfunction (ED), one of the most common male sexual disorders, is defined as the inability to achieve and/or maintain an adequate penile erection for sexual activity (6). Penile erection is affected by many factors, such as hormonal, neurogenic, vascular, and psychogenic factors (6,7). Various methods have been used to measure the presence and severity of ED. The International Index of Erectile Function (IIEF) questionnaire is a 15-item self-report survey that has become the primary method in ED studies (8). The IIEF-5 questionnaire is a variant of the IIEF developed for the same purpose that can be administered in a shorter time (9).

ED is associated with different diseases. The frequency of ED increases with chronic diseases, such as chronic lung diseases, endocrine diseases, cardiovascular diseases, and psychiatric disorders (10). However, the presence of ED is an early warning of coronary artery and peripheral vascular diseases (11). A disease associated with ED is ISSHL (12,13). Although there are limited studies on this relationship in the literature, in a study conducted to examine the relationship between ED and ISSHL, the incidence of ED in ISSHL patients was 1.96 times higher than in patients without this disease (12).

This study investigated the frequency of ED in men with ISSHL and the response of ED to ISSHL treatment in these men, prospectively.

METHODS

This prospective-case control study was conducted on patients and volunteers between November 2021 and May 2022 with the confirmation of the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (decision no: 177948, date: 08.09.2021). All individuals signed an informed consent form.

Populations, Inclusion, and Exclusion Criteria

All subjects of this study applied to the Otorhinolaryngology Departments of Cerrahpaşa Faculty of Medicine Hospital and University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital. Married and sexually active male patients with ISSHL and healthy volunteers were included in this study. The control group consisted of sexually active healthy men. Patients with unilateral sudden idiopathic sensorineural hearing loss were included in the study group. All the patients in this study applied within the first 3 days of the onset of hearing loss.

Exclusion criteria were determined to include conditions that may be risk factors for sexual dysfunction: being over 50 years of age, obese (body mass index ≥30), alcohol-dependent, smoker; having a history of mental, sexual, and psychiatric disorders, chronic disease and atherosclerosis (14). Additionally, the individuals under 18 years of age, the individuals with acute or chronic infection in the affected ear, the individuals with a history of ear surgery, the patients whose etiologic cause of sudden hearing loss was determined during the study period and the individuals who regularly used any drug in the past 3 months were excluded from the study.

One of the aims of this study was to investigate the effect of SSHL treatment on sexual dysfunction. Therefore, in the pure tone audiometry (PTA) test, a gain of more than 15 dB on the average of 6 frequencies was determined as the treatment success criterion (15). The patients who could not achieve this success with treatment in the 6th month of the disease were excluded from the study.

Sample Size and Sampling Technique

The minimum (min) number of subjects was calculated based on the study of Bakır et al. (16). The min subject number was determined as 19 for each group with a 95% confidence interval (5% acceptable error).

In this study, a stratified sampling method was used. People who applied to our clinic every day were divided into 2 subgroups; the patients with SSHL and people with normal hearing. Four participants were randomly selected every day from these layers using a computer program. The individuals having any exclusion criteria for the study were excluded from the subgroups.

Procedures and Data Collection

Study Design

Day 0 (initial): Detailed anamnesis of the participants were taken. The full-otorhinolaryngological examination, audiological tests, blood tests, and imaging tests for the etiology of sudden hearing loss were performed. Patients with sensorineural hearing loss of more than 30 decibels for at least 3 consecutive frequencies were included in the study group. The pure tone mean (PTM) was determined by averaging the hearing thresholds at frequencies of 250, 500, 1,000, 2,000, 4,000, and 8,000 Hz. The healthy individuals who the normal audiological test was included in the control group. The treatments of ISSHL were arranged. IIEF-5 questionnaires were administered to the participants.

Day 180 (6th month): The PTA tests and questionnaires of the patients were repeated. Patients with hearing gain of less than 15 dB and a PTM value of less than 75 dB were considered treatment failures (17). Patients who did not achieve success with the treatment were excluded from the study.

Methods

Clinical Examinations

The full-otorhinolaryngological was examined using 0° and 70° endoscopes by the first otorhinolaryngology specialist. Patients whose anamnesis and tuning fork tests were compatible with sudden hearing loss were referred to the audiology department.

Audiological Tests

Patients from the clinic were sent to the audiology department for audiological tests without specifying their clinical presentations. PTA tests were performed blindly in the same center, in the same cabin, by the same person with the same device.

Laboratory Tests

A complete blood count was performed on each patient. Enzyme-linked ımmunosorbent assay test was applied for evaluating viruses that may be involved in SHL etiology (varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, hepatitis B virus, hepatitis C virus, mumps, rubella, herpes simplex virus 1 and 2). A full-biochemistry panel was examined, including biochemistry parameters for kidney functions, liver functions and thyroid functions, coagulometry parameters, C-reactive protein (CRP), glucose and HbA1C, anions, and cations.

Radiologic Tests

Brain magnetic resonance imaging (1.5 Tesla) with gadolinium was performed on each patient for etiologic investigation. Evaluation of the acquired images was made by the same expert radiologist.

The Survey

The quality of sexual life was examined using the IIEF-5 questionnaire. The IIEF-5 questionnaire is frequently used to evaluate male sexual function. This survey consists of 5 questions, the first 4 questions are for ED and the last question is for sexual satisfaction (18). All questions were scored from 1 to 5 according to the degree of dysfunction (5= no dysfunction, 4= mild dysfunction, 3= mild-to-moderate, 2= moderate, and 1= severe). More detailed investigations should be conducted with the suspicion of ED in people with a questionnaire score of 21 or less. The low scores indicate higher grades of dysfunction (9,18).

The questionnaire was administered to the patients blindly, without knowing the participant's group, by the second male otorhinolaryngology specialist within 15 min. Additionally, the IIEF-5 questionnaire was grouped into the first 4 questions (Q1-Q4) and the last question (Q5). The initial (pretreatment) and 6th month (posttreatment) IIEF-5 scores, the first 4 questions (IIEF-5_{Q1-Q4}) scores, and the last question (IIEF-5_{Q5}) scores of the control group and SSHL patients were determined. Additionally, the number of subjects with suspected ED in the study groups according to the results of the questionnaire was also determined.

The Treatments

All patients received a combination of intratympanic steroid (ITS) therapy and hyperbaric oxygen therapy (HBOT). On the 1st, 3rd, 5th, 7th, 14th, and 30th days of ISSHL diagnosis, 6 doses of ITS treatment were administered once a day.

HBOT was applied at 2.5 atm pressure for 2 h a day for 20 sessions, starting from the first day of diagnosis. Intratympanic injections were performed using a binocular otology microscope. Cotton impregnated with lidocaine (Xylocaine 10 mg/dose spray) was placed over the tympanic membrane of the affected ear. After 10 min, the patient was positioned in the supine position. The head was rotated 45 degrees toward the unaffected ear. Cotton was removed from the external ear canal and visualization was achieved

to see the 4 quadrants of the tympanic membrane. First, a perforation located in the anterior superior quadrant of the tympanic membrane was created using a 27 gauge needle. Then, 1-mL dexamethasone (8 mg/2 mL) was delivered to the middle ear by puncture in the anterior inferior quadrant. After the injection, the patient remained in the same position and avoided speaking, yawning, and swallowing for 20 min.

Statistical Analysis

The calculation of the minimal subject number was performed using the G*Power program version 3.1 (19). SPSS Version 22.0 (SPSS Inc., USA) was used for statistical analysis. Normal distribution and homogeneity of data were analyzed with the Kolmogorov-Smirnov test and Levene's tests, respectively. Mann-Whitney U test, Wilcoxon signed-ranks test, and Pearson chi-square test were used in the statistical analysis of the survey results. The significance level was set as a p-value less than 0.05 ($p<0.05$).

RESULTS

Forty-four SSHL patients were included in this study, and 19 (43.18%) of them formed the study group in accordance with the study criteria. The study group consisted of 12 (63.2%) male and 7 (36.8%) female patients, and the control group consisted of 9 (47.4%) male and 10 female (52.6%) participants. There was no difference between the groups in terms of subject gender (Pearson chi-square test, p=0.328). The mean ages of the groups were 34.53±7.48 [median= 31, min: 24-maximum (max): 46] for the SSHL patients and 30.95±8.74 (median= 31, min: 18-max: 48) for the control group. No significant difference was found between the groups in terms of subject age (Mann-Whitney U test, p=0.236).

In the PTA result analysis, the initial PTM of the patients was 48±16.479 (min: 30-max: 90) dB. In the 6th month, the PTM was 24.368±17.676 (min: 2-max: 70) dB. In the patients, mean gain with treatment was 23.632±7.522 (min: 15-max: 40) dB (Figure 1).

In the evaluation of survey results, the initial IIEF-5 and IIEF-5_{Q1-Q4} scores of the patients were significantly lower than those of the control group (p=0.003, p=0.003, respectively). The initial IIEF-5_{Q5} scores of patients were lower than that of the control group. However, there was no significant difference between the groups in terms of the IIEF-5_{Q5} scores (p=0.937). The 6th month IIEF-5 and IIEF-5_{Q1-Q4} scores of the patients were significantly higher than the initial scores (p=0.034, p=0.016). The 6th-month IIEF-5_{Q5} score was higher than the initial score. However, no significant difference was found between the groups in terms of the IIEF-5_{Q5} scores (p=0.157). In the comparison of the post-treatment IIEF-5 survey results of SSHL patients with the IIEF-5 survey results of the control group, no significant difference was found between the groups (p>0.05) (Table 1).

In the IIEF-5 survey results, ED was suspected in 8 patients (42.1 %) in the control group, 17 patients (89.5%) in pretreatment ISSHL patients, and 8 patients (42.1%) in posttreatment ISSHL patients. When the groups were examined according to the presence of ED suspicion in the IIEF-5 questionnaire results, it was seen that the frequency of ED suspicion was significantly higher in ISSHL patients compared to the control group (p=0.002). After ISSHL treatment, the number of patients with suspected ED was significantly less compared to the pre-treatment period [Pearson chi-square test, value =9.471; degrees of freedom (df)=1; p=0.002] and the significant difference between pretreatment ISSHL patients and the control group disappeared with ISSHL treatment (Pearson chi-square test, value=0.000; df=1; p=1.000) (Table 2).

DISCUSSION

SSHL is a complex and controversial disease with its pathophysiology. Despite all advances in medicine, the cause of the disease cannot be determined in 90% of SSHL patients and it is called ISSHL (20). Idiopathic SSHL is related to many diseases, especially cardiovascular diseases (2,4). ED is one of the most common sexual disorders in men (5,10,21). ED, the frequency of which is gradually increasing due to lifestyle changes, is associated with many diseases (5-7). In this study, which is the first prospective study in English literature, we examined the relationship between these two diseases, which are associated with many conditions.

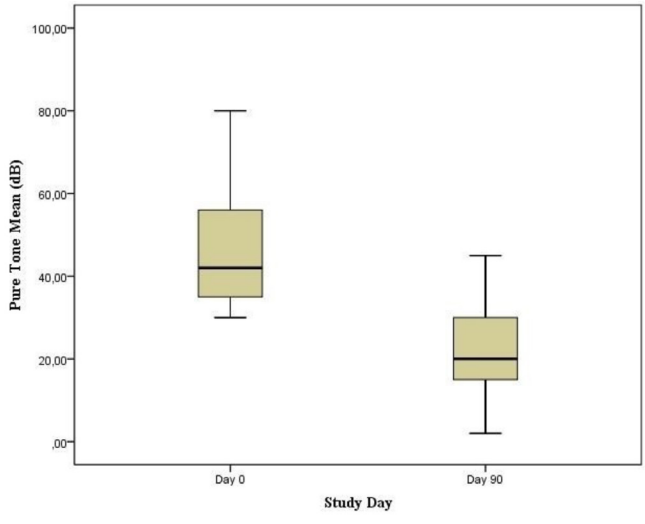

Figure 1. Evaluation of pure tone means by study days

Table 1. Analysis of IIEF-5 survey scores in patients with SSHL and healthy individuals (control group)

Questionnaire	Mean ± standard deviation (median)			p		
	Control group	Pretreatment SSHL patients	Posttreatment SSHL patients	Pretreatment vs. control	Posttreatment vs. control	Pretreatment vs. posttreatment
IIEF-5	21.05±3.837 (22)	18.11±2.826 (18)	20.89±3.725 (22)	0.003*	0.779	0.034†
$IEFF_{Q1-Q4}$	16.894±3.142 (18)	14±2.582 (13)	16.684±3.02 (18)	0.003*	0.612	0.016†
$IEFF_{Q5}$	4.053±0.911 (4)	4.1±0.737 (4)	4.21±0.63 (4)	0.937	0.781	0.157

SSHL: Sudden sensorineural hearing loss, IIEF: International Index of Erectile Function, *Mann-Whitney U test, $p<0.05$, †Wilcoxon signed-ranks test, $p<0.05$

Table 2. Analysis of the number of participants with suspected erectile dysfunction

Groups	Suspected erectile dysfunction* +, n (%)	Suspected erectile dysfunction* -, n (%)	p
Control	8 (42.1%)	11 (57.9%)	0.002†
Pretreatment SSHL patients	17 (89.5%)	2 (10.5%)	

SSHL: Sudden sensorineural hearing loss, IIEF: International Index of Erectile Function, *Suspected erectile dysfunction, the participant with an IIEF-5 survey score of 21 or less, †Pearson chi-square test, value=9.471; df=1; $p<0.05$

Because of our study, we found that the IIEF-5 questionnaire scores were significantly lower in ISSHL patients compared to the control group and the number of patients with suspected ED was significantly higher in this patient group ($p<0.05$). We found that the sexual disorders we detected in these patients responded to SSHL treatment, and there was no statistically significant difference between ISSHL patients and the control group, both in IIEF-5 scores and in the number of patients with suspected ED after treatment ($p<0.05$).

Normal sexuality, especially penile erection, is a complex process that is affected by hormone levels, neurogenic and psychogenic factors, vascular and hemodynamic factors (5). The disorders that may occur in all these factors result in sexual dysfunction (5,10). ED, which affects psychosocial health and QoL, is classified as organic, psychogenic, or mixed depending on its etiology (5,7,10). Endothelial dysfunction and vascular causes are responsible for most organic EDs (5,7,10). Therefore, ED is considered as an early warning for heart attack and stroke (10,11). The causes of psychogenic ED are psychological diseases such as anxiety, depression, and disorders in psychosocial life (5,7).

ED, 80% of which is due to organic etiologies, is associated with many diseases such as sleep disorders, inflammatory diseases, chronic diseases, obesity, allergic rhinitis, smoking, and alcohol addiction (5,7,10). In terms of otorhinolaryngology diseases, the relationship between ED and vertigo, obstructive sleep apnea, Meniere's disease, allergic rhinitis, and hearing loss has been reported in previous studies (16,22-24). In different studies conducted with patients with sensorineural hearing loss, it was determined that the sexual health of these patients was poorer compared to patients with normal hearing (16,23). In one of these studies, it was shown that while orgasmic function, sexual desire, and general satisfaction were negatively affected in patients with bilateral sensorineural hearing loss, erectile function, and sexual satisfaction was not affected (23).

To explain the pathophysiology of SSHL, vascular causes have been investigated in previous studies and possible causes such as traumatic, autoimmune, infectious, and metabolic events (1-4). The fact that the inner ear is end-organ with blood flow from a single artery, spontaneous recovery seen in patients with SSHL, ischemic cochlear histological findings shown by previous studies, and the increase in the frequency of coronary artery disease, stroke, and peripheral vascular disease in SSHL patients support vascular causes in the pathophysiology of SSHL (2,25,26). If SSHL is associated with these vascular diseases, due to possible microvascular causes in its pathophysiology, it may also be associated with ED, another disease in which vascular causes play a role in its etiology. Additionally, ISSHL patients have a poor QoL and impaired psychosocial status, which cause ED (5,7,10,27).

There are large-population-based retrospective studies examining the relationship between ED and SSHL (12,13). In

these studies, it was reported that SSHL is associated with ED, and SSHL is a risk factor for ED (12,13). However, there is no prospective study examining this relationship in English literature. We planned this prospective study to examine the relationship between ED and ISSHL. The IIEF questionnaire is a method that questions one-month sexual life (8). It is the most used in ED studies and is accepted as a standard for these studies (8,18). However, ED was defined by the National Institutes of Health as the penile erection inability for at least 6 months (7). The IIEF-5 is a shorter version of the IIEF survey and examines 6 months (7,17). Therefore, the IIEF-5 questionnaire was used in this study with the thought that it would be more appropriate. We included known factors that may cause ED among the exclusion criteria of our study and tried leaving only ISSHL disease as a possible cause of ED to ensure optimal standardization (5,7,10,14). Additionally, we excluded possible etiologies by using the widest range of laboratory and imaging tests specified in the literature and accepted SSHL patients as ISSHL patients (1,27). The primary treatment for sudden hearing loss is steroid therapy and intratympanic application of this treatment can be chosen as the primary treatment (28,29). In a previous study, it was shown that better results were obtained with ITS therapy in PTA average compared to systemic steroid therapy (29). Additionally, an advantage of ITS is that the systemic side effects of steroids are much less (28). Regardless of the route of steroid treatment, its combination with HBOT increases the success of the treatment (15). In this study, we applied dexamethasone intratympanically and combined the treatment with HBOT, in accordance with the literature, so that the systemic effects of the steroid would not affect our study (15,28,29).

In our study, the IIEF-5 and $IEFF_{Q1-Q4}$ scores were significantly lower in ISSHL patients before treatment compared to the control group (p=0.003; p=0.003, respectively). Additionally, the number of patients with suspected ED according to the IIEF-5 questionnaire was significantly higher in ISSHL patients before treatment compared to the control group (p=0.002). According to the IIEF-5 questionnaires repeated after the treatment of ISSHL patients, IIEF-5 and $IEFF_{Q1-Q4}$ scores were significantly higher than the pre-treatment values, and there was no significant difference compared with the control group scores (p=0.034; p=0.016, respectively). Additionally, according to the IIEF-5 questionnaire repeated in the post-treatment period, the number of patients with suspected ED was significantly less than before the treatment (p=0.002), and there was no significant difference compared with the control group (p=1.000). The results of our study are compatible with the literature and support the vascular hypothesis in the etiology of SSHL. In a study by Soylu Ozler and Ozler (23), many components of sexuality were negatively affected in patients with sensorineural hearing loss, however, there was no negative effect on erectile function and sexual intercourse satisfaction. In the study of Bakır et al. (16), both erectile function and sexual satisfaction were negatively affected in patients with sensorineural hearing loss. Unlike the previous studies, this study reported that the presence of sensorineural hearing loss has a negative effect on erectile function ($IIEF\text{-}5_{Q1-Q4}$) and did not make a difference in sexual satisfaction ($IIEF\text{-}5_{Q5}$). Different results may be due to the difference between the pathophysiology of SSHL and sensorineural hearing loss. Our results, which differ from those of previous studies, may be due to the difference between the pathophysiology of SSHL and sensorineural hearing loss. While vascular disorders in the pathophysiology of ED are involved in the etiology of ISSHL, non-vascular cochlear and neuronal disorders are prominent in sensorineural hearing loss (30).

For the first time in the literature, we demonstrated the relationship between ED and ISSHL disease, there are quite a few studies in the literature about this relationship, with a prospective study. However, there are some limitations to our study. The first of these limitations is the limited number of subjects in our study. We included a limited number of subjects in the study because of the prospective design of the study. However, we calculated this number statistically (19). The second limitation is that the IIEF-5 test cannot directly diagnose ED. However, the IIEF-5 form is used reliably by many clinics in the diagnosis of sexual dysfunction and in determining whether there is improvement after the treatment given, because of its high accuracy rate (18). The final limitation of this study stems from the definition of ISSHL disease. Although we have ruled out many diseases that cause SSHL with many tests, patients diagnosed with ISSHL today may be diagnosed with a disease in the future.

CONCLUSION

ISSHL is not just an otological problem. ISSHL may be accepted as a risk factor for ED. ISSHL can affect sexual life and therefore QoL. There is a need to repeat the obtained data with larger sample numbers and to conduct molecular studies on the pathophysiology of ED seen in ISSHL patients.

ETHICS

Ethics Committee Approval: This prospective-case control study was conducted on patients and volunteers between November 2021 and May 2022 with the confirmation of the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (decision no: 177948, date: 08.09.2021).

Informed Consent: All individuals signed an informed consent form.

Authorship Contributions

Surgical and Medical Practices: D.Ç., Concept: D.Ç., Design: D.Ç., Data Collection or Processing: D.Ç., S.U., Analysis or Interpretation: S.U., Literature Search: D.Ç., Writing: D.Ç., S.U.

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

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

REFERENCES

1. Stachler RJ, Chandrasekhar SS, Archer SM, Rosenfeld RM, Schwartz SR, Barrs DM, et al. Clinical practice guideline: sudden hearing loss. Otolaryngol Head Neck Surg 2012;146(3 Suppl):S1-35.
2. Lammers MJW, Young E, Westerberg BD, Lea J. Risk of Stroke and Myocardial Infarction After Sudden Sensorineural Hearing Loss: A Meta-Analysis. Laryngoscope 2021;131:1369-77.
3. Alexander TH, Harris JP. Incidence of sudden sensorineural hearing loss. Otol Neurotol 2013;34:1586-9.
4. Tsuzuki N, Wasano K, Oishi N, Hentona K, Shimanuki M, Nishiyama T, et al. Severe sudden sensorineural hearing loss related to risk of stroke and atherosclerosis. Sci Rep 2021;11:20204.
5. Chen L, Shi GR, Huang DD, Li Y, Ma CC, Shi M, et al. Male sexual dysfunction: A review of literature on its pathological mechanisms, potential risk factors, and herbal drug intervention. Biomed Pharmacother 2019;112:108585.
6. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA 1993;270:83-90.
7. Irwin GM. Erectile Dysfunction. Prim Care 2019;46:249-55.
8. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997;49:822-30.
9. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999;11:319-26.
10. Salonia A, Bettocchi C, Boeri L, Capogrosso P, Carvalho J, Cilesiz NC, et al. European Association of Urology Guidelines on Sexual and Reproductive Health-2021 Update: Male Sexual Dysfunction. Eur Urol 2021;80:333-57.
11. Pozzi E, Capogrosso P, Boeri L, Belladelli F, Baudo A, Schifano N, et al. Longitudinal Risk of Developing Cardiovascular Diseases in Patients With Erectile Dysfunction-Which Patients Deserve More Attention? J Sex Med 2020;17:1489-94.
12. Hsu HT, Chen JY, Weng SF, Huang KH, Lin YS. Increased risk of erectile dysfunction in patients with sudden sensorineural hearing loss: a nationwide, population-based cohort study. Otol Neurotol 2013;34:862-7.
13. Keller JJ, Chen YK, Lin HC. A case-control analysis on the association between erectile dysfunction and sudden sensorineural hearing loss in Taiwan. J Sex Med 2012;9:1411-7.
14. Sooriyamoorthy T, Leslie SW. Erectile Dysfunction. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562253/
15. Yilmaz YZ, Usaklioglu S. Comparison of Treatment Modalities in Adult Idiopathic Sudden Hearing Loss: A 5-year Outcome from a Tertiary Referral Center. Med Bull Haseki 2022;60:133-7.
16. Bakır S, Penbegül N, Gün R, Yorgancilar E, Kiniş V, Özbay M, et al. Relationship between hearing loss and sexual dysfunction. J Laryngol Otol 2013;127:142-7.
17. Rajati M, Ghasemi MM, Sharifian MR, Nourizadeh N, Yousefi R, Hosseinpoor M. Intratympanic Steroid for the Management of Sudden Hearing Loss: Introduction of a Tapering Method. Iran J Otorhinolaryngol 2022;34:9-16.
18. Turunç T, Deveci S, Güvel S, Peşkircioğlu L. The Assessment Of Turkish Validation With 5 Question Version Of International Index Of Erectile Function (IIEF-5). Turkish J Urol 2007;33:45-9.
19. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175-91.
20. Prince ADP, Stucken EZ. Sudden Sensorineural Hearing Loss: A Diagnostic and Therapeutic Emergency. J Am Board Fam Med 2021;34:216-23.
21. Irfan M, Hussain NHN, Noor NM, Mohamed M, Sidi H, Ismail SB. Epidemiology of Male Sexual Dysfunction in Asian and European Regions: A Systematic Review. Am J Mens Health 2020;14:1557988320937200.
22. Zapata C, López-Escámez JA. Estudio piloto de la salud sexual en pacientes con enfermedad de Ménière [A pilot study of sexual health in patients with Ménière's disease]. Acta Otorrinolaringol Esp 2011;62:119-25.
23. Soylu Ozler G, Ozler S. Quality of Social and Sexual Life in Males with Hearing Loss. J Int Adv Otol 2013;9:211-8.
24. Cakan D, Ozturk E, Usaklıoglu S. A Prospective Analysis of the Relationship between Sexual Dysfunction and Allergic Rhinitis in Men. Med Bull Haseki 2022;60:234-9.
25. Quaranta N, De Ceglie V, D'Elia A. Endothelial Dysfunction in Idiopathic Sudden Sensorineural Hearing Loss: A Review. Audiol Res 2016;6:151.
26. Fasano T, Pertinhez TA, Tribi L, Lasagni D, Pilia A, Vecchia L, et al. Laboratory assessment of sudden sensorineural hearing loss: A case-control study. Laryngoscope 2017;127:2375-81.
27. Sano H, Okamoto M, Ohhashi K, Iwasaki S, Ogawa K. Quality of life reported by patients with idiopathic sudden sensorineural hearing loss. Otol Neurotol 2013;34:36-40.
28. Sialakis C, Iliadis C, Frantzana A, Ouzounakis P, Kourkouta L. Intratympanic Versus Systemic Steroid Therapy for Idiopathic Sudden Hearing Loss: A Systematic Review and Meta-Analysis. Cureus 2022;14:e22887.
29. Qiang Q, Wu X, Yang T, Yang C, Sun H. A comparison between systemic and intratympanic steroid therapies as initial therapy for idiopathic sudden sensorineural hearing loss: a meta-analysis. Acta Otolaryngol 2017;137:598-605.
30. Cunningham LL, Tucci DL. Hearing Loss in Adults. N Engl J Med 2017;377:2465-73.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:348-355
DOI: 10.4274/BMJ.galenos.2022.2022.8-6

Research

Evaluation of Psychosocial Symptoms in Adolescents During the COVID-19 Pandemic in Turkey by Comparing Them with the Pre-pandemic Situation and Its Relationship with Quality of Life

Türkiye'de COVİD-19 Pandemisi Döneminde Ergenlerde Psikososyal Belirtilerin Pandemi Öncesi Durumla Karşılaştırılması ve Yaşam Kalitesi ile İlişkisinin Değerlendirilmesi

Uğur Tekin

University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Child and Adolescent Psychiatry, İstanbul, Turkey

ABSTRACT

Objective: This study investigated the changes in psychosocial symptoms in adolescents in Turkey during the pandemic and their relationship with the quality of life (QoL).

Methods: A total of 118 adolescents reached via Google e-forms, participated in the study. The affective reactivity index-parent-report, hyperactivity/impulsivity and inattention sub-scale of Turgay-DSM-IV-S, revised child anxiety and depression scales-parent version, and the pediatric QoL inventory were utilized for psychosocial symptoms' evaluation.

Results: Compared to the pre-pandemic period, a significant increase in adolescents' attention problems, hyperactivity/impulsivity, and irritability, and a decrease in general, psychosocial, and physical QoL were found. The psychosocial and total QoL scores showed moderate/high levels of negative correlations with irritability, attention problems, depression, separation anxiety, generalized anxiety, panic, social anxiety, and obsessive-compulsive disorder scores.

Conclusion: The pandemic process in Turkey has adversely affected the mental health of adolescents. In increased psychosocial symptoms in this process are associated with lower QoL.

Keywords: COVID-19 pandemic, psychosocial symptoms, adolescent, quality of life

ÖZ

Amaç: Bu çalışma, Türkiye'de pandemi döneminde ergenlerde psikososyal belirtilerde meydana gelen değişiklikleri ve yaşam kalitesi (YK) ile ilişkisini araştırmayı amaçlamıştır.

Gereç ve Yöntem: Çalışmaya Google e-formları aracılığıyla ulaşılan toplam 118 ergen katılmıştır. Afektif reaktivite indeksi-ebeveyn formu, Turgay-DSM-IV-S hiperaktivite/dürtüsellik ve dikkatsizlik alt ölçekleri, çocuklarda anksiyete ve depresyon ölçeği-yenilenmiş ebeveyn formu ve pediatrik YK envanteri psikososyal belirtilerin değerlendirilmesi için kullanılmıştır.

Bulgular: Pandemi öncesi döneme göre ergenlerde dikkat sorunları, hiperaktivite/dürtüsellik ve irritabilitede anlamlı artış; toplam, psikososyal ve fiziksel YK'lerinde düşüş saptandı. Psikososyal ve toplam YK puanları, sinirlilik, dikkat sorunları, depresyon, ayrılık kaygısı, yaygın kaygı, panik, sosyal kaygı ve obsesif kompulsif bozukluk puanları ile orta/yüksek düzeyde negatif korelasyon gösterdi.

Sonuç: Türkiye'de pandemi süreci ergenlerin ruh sağlığını olumsuz etkilenmiştir. Ve bu süreçte artmış olan psikososyal semptomlar düşük YK ile ilişkilidir.

Anahtar Kelimeler: COVİD-19 pandemisi, psikososyal belirtiler, ergenlik, yaşam kalitesi

Address for Correspondence: Uğur Tekin, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Child and Adolescent Psychiatry, İstanbul, Turkey
Phone: +90 543 450 52 30 E-mail: drutekin@hotmail.com ORCID ID: orcid.org/0000-0001-6720-4292

Cite as: Tekin U. Evaluation of Psychosocial Symptoms in Adolescents During the COVID-19 Pandemic in Turkey by Comparing Them with the Pre-pandemic Situation and Its Relationship with Quality of Life. Med J Bakirkoy 2022;18:348-355

Received: 15.08.2022
Accepted: 14.09.2022

INTRODUCTION

The coronavirus disease-2019 (COVID-19), that started in China in November 2019 and spread out to the world, has rapidly become a global problem and was announced as a pandemic by the World Health Organization in March 2020 because of its alarming rate of spread (1). Starting from the day it first appeared, countries have taken multiple precautions such as social isolation, quarantine, lockdown, social distance measures, and mask requirements to reduce the spread of COVID-19 (2,3). Because of the measures taken in this process, many restrictions affecting social life such as the closure of schools and workplaces, working from home, online training, encouraging staying at home, and closing of sports facilities and entertainment venues have occurred. The threat, panic, and fear created by these measures and the pandemic itself have created a significant change in the daily lives of people from all age groups compared to the pre-pandemic period (4). The effects of these changes brought by the pandemic on children and adolescents' mental health and well-being have been a concern since the early days.

The United Nations has reported that the pandemic disrupts mental health and physical health. In an online study conducted in China during the early stages of the outbreak, 320 children were investigated in terms of behavioral and emotional responses to the pandemic, and the most common problems were reported as distractions, irritability, and worry of asking questions about the pandemic, anxiety, and depression (4). In another study conducted in the United Kingdom to evaluate difficulties in children and youth with an online survey, it was shown that the younger age group had higher levels of anxiety and fear (5). During adolescence, when physical, psychological, and social changes and development occur, adolescents may experience greater difficulty in coping with crises because their resilience and coping skills are not yet sufficiently developed (6,7). Additionally, peer relationships become more important due to increased social sensitivity during adolescence. The quality of peer relationships plays a role in shaping self-concept and guiding behavior (8). Positive peer relationships in this developmental period provide social and emotional support, which is protective in terms of psychiatric disorders. Studies have shown that the biggest concerns of adolescents during the COVID-19 pandemic are not related to catching the virus or getting sick but to a decrease in social interactions (9).

It is known that COVID-19 causes a milder infection in adolescents compared to adults (4). However, in the child and adolescent age group, who are already at higher risk of developing psychological troubles compared with adults, the outcomes of the pandemic on mental health become even more significant, due to various vulnerability factors (10,11). Outbreaks can be a source of adverse childhood experiences (ACE) that negatively affect development by creating the risk of getting sick, quarantine, social isolation, and high stress level in parents. ACEs are defined as traumatic or stressful incidents in childhood, such as neglect, abuse, violence, and pandemics, that adversely affect individual and social health, neural development, physical and mental health, and working capacity in adulthood (12,13). Although the studies have shown that the pandemic causes emotional and behavioral changes in children and adolescents, the effects of the pandemic on adolescent mental health have been relatively less focused on.

It has also been reported that children and adolescents experience a significant reduction in their quality of life (QoL) because of the challenges and changes brought about by COVID-19 (14). Nevertheless, there is limited information in the literature about the relationship between a deterioration in the QoL and psychosocial and behavioral complaints in adolescents. With a better understanding of this issue through studies, groups with a high risk of developing psychosocial problems despite future pandemics, such as the COVID-19 pandemic, will be better known and have an opportunity to be better intervened. Moreover, because of the increase in knowledge on this subject, it may be possible to prevent, improve and rehabilitate the negative psychosocial consequences that may develop.

Countries have taken different levels of precaution against the COVID-19 pandemic. There are different opinions about the effects of these measures on mental health (15-17). However, the general view is that stricter COVID-19 policy restrictions are associated with worse mental health because they reduce social contact and increase physical distance. Stricter measures are thought to negatively affect mental health (17). Due to the differences in the measures taken, there will likely be differences in the effects on mental health. Turkey was a country that took strict measures to reduce the spread of the virus. Some of the early and radical measures implemented in this process in Turkey were as follows; education was suspended, then online education was started, schools, gyms, places of worship, restaurants, shopping malls, entertainment venues, restaurants were closed, foreign entry-exit ban was applied, long-term and comprehensive quarantine and curfew were applied. The long-term curfew under 18s and over 65s and the prohibition of the use of urban public transportation may have affected the mental health of these age groups more negatively.

Therefore, when examining the effects of the pandemic on mental health, considering the variation in COVID-19 policy restrictions of the countries, it will provide more accurate results.

Consequently, in this study, we investigated the changes in anxiety, depression, irritability, and attention deficit and hyperactivity symptoms in adolescents with the pandemic and their relationship with QoL.

METHODS

Participants and Procedures

A total of 118 adolescents and their families from different cities of Turkey, reached via Google e-forms, participated in the study between May and June 2021, when the 3rd wave of the pandemic was effective in Turkey. After the participants were given detailed information about the research and informed that their participation would be voluntary, the sociodemographic data form and scales were applied to the volunteers. Participants were asked to fill in the applied scales and questionnaires twice. The 1st was according to the pandemic conditions; the second was according to the period before the pandemic started. Ethical consent and approval (Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee - decision no: 2021-10-03, date: 17.05.2021) of the study and written informed consent were obtained.

Sociodemographic data form: In the form, information about gender, age, school-education status, parents, and family characteristics were collected. Participants with a previous history of psychiatric illness were excluded from the study.

Affective reactivity index-parent-report (ARI-P): to measure the irritability of level participants, the ARI-P scale was used. The ARI-P consists of six items evaluating irritable attitudes, including the frequency, course, and threshold of the action. A 3-point Likert-type measure ranging from "(0) not true" to "(2) definitely true" is used to survey every item, with the overall score ranging from 0 to12. Chronic irritability was specified by a higher score. The validity and reliability study of ARI for the Turkish form was conducted (ARI-p: α=0.83) (18).

Turgay DSM-IV based children and adolescents behavior disorders screening and rating scale (Turgay-DSM-IV-S): The Hyperactivity/impulsivity and inattention levels of subjects were assessed using the scores of the parents for their children on the Turgay-DSM-IV-S that is a broadly used scale for attention-deficit/hyperactivity problems. It is based on the DSM-IV diagnostic criteria and evaluates hyperactivity/impulsivity (9 items), inattention (9 items), opposition/defiance (8 items), and conduct disorder (15 items). The items are scored by defining a severity rating for every symptom on a 4-point likert-type measure (namely: 0 not at all, 1 just a little, 2 quite a bit, 3 very much). Hyperactivity/impulsivity and inattention sub-scale were used in this study (19).

Revised children anxiety and depression scales, parent form (RCADS-P): RCADS-P is a questionnaire with 47-items designed to assess depression and anxiety symptoms in children and adolescents based on DSM-IV diagnostic criteria. Reply choices are based on 4-point Likert-type scales (0= never, 1= sometimes, 2= often, and 3= always). The measure has 6 sub-scale scores [separation anxiety disorder, social phobia, obsessive-compulsive disorder (OCD), panic disorder, generalized anxiety disorder, major depressive disorder], total anxiety score (total of five anxiety subscales), and total anxiety and depression score. Gormez et al. (20) conducted a validity and reliability study of the Turkish form of RCADS-P.

The pediatric quality of life inventory (PedsQL): PedsQL filled out by parents was used to assess the QoL and functioning. The PedsQoL evaluates the health-related QoL in child and adolescent. It is calculated in three scores psychosocial health, physical health, and total QoL overall score. PedsQL-psychosocial sub-scale comprising 15 items, examines areas of emotional functioning, social functioning, and school functioning. A validity and reliability study of the Turkish form for adolescents has been conducted (21).

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences Statistics 22 statistical software package program. The statistical data for the groups were expressed using the mean and standard deviation. Comparisons between the pre-pandemic and the pandemic periods were compared using the Wilcoxon signed-rank test. The correlations between QoL scores and psychosocial symptom scores were analyzed using the Spearman rho correlation coefficient. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 118 adolescents, 77 (65%) girls, and 41 (35%) boys were included in the study. The mean age of the sample was 13.2 (±2.1) years. The sociodemographic characteristics of the sample are summarized in Table 1.

Psychosocial symptoms and QoL scores between the pre-pandemic and the pandemic periods were compared using the Wilcoxon signed-rank test since the data were not

normally distributed. Comparison analysis are presented in Table 2. In the pandemic, the irritability levels evaluated with ARI-parent-report were significantly increased compared with the pre-pandemic period (Z=-6.285, p<0.001). In the Turgay attention deficit hyperactivity disorder (ADHD) scale, attention and hyperactivity/impulsivity problems increased significantly in the pandemic compared to the pre-pandemic period (Z=-6.339, p<0.001; Z=-4.245, p<0.001, respectively). A statistically significant increase was observed in all depression, anxiety, and OCD scores evaluated with the RCADS-parent report compared with the pre-pandemic period (Table 2). Additionally, in the parent report Ped. QoL scale, a statistically significant decrease was observed in the health-related psychosocial and physical QoL in the pandemic compared to the pre-pandemic period (Z=-6.944, p<0.001; Z=-4.453, p<0.001, respectively).

Table 1. Sociodemographic variables of the participants

	n (%)
Sex	
Male	41 (35%)
Female	77 (65%)
Age (mean ± SD) (y)	13.2±2.1 Min =10 Max =17
School	
Elementary school	81 (69%)
High school	37 (31%)
SES	
Low	12 (10%)
Middle	45 (38%)
High	61 (52%)
Maternal	
Age (mean ± SD) (y)	41.3±5.5
University education*	50 (42%)
Employment**	47 (40%)
Paternal	
Age (mean ± SD) (y)	45.2±6.7
University education*	61 (52%)
Employment**	116 (98%)
Divorced family	5 (4.2%)

SES: Socio-economic status, SD: Standard deviation, y: Years, Min: Minimum, Max: Maximum

*Number of parents with university or higher education

**Number of employed parents

The correlations between QoL scores and psychosocial symptom scores were analyzed using the Spearman rho correlation coefficient test. The psychosocial QoL and total QoL scores showed moderate/high levels of negative correlations with irritability, attention problems, depression, separation anxiety, generalized anxiety, panic, social anxiety, and OCD scores. Additionally, they were weakly negatively correlated with the hyperactivity/impulsivity score. Physical health QoL score was weakly negatively correlated with all psychosocial symptom scores except generalized anxiety. There was no correlation with generalized anxiety. The results of the correlation analyzes are summarized in Table 3.

DISCUSSION

In this study, the changes due to the pandemic in the mental health and perceived health-related QoL of 10-17-year-old adolescents in Turkey were investigated. Our findings showed that the general QoL of adolescents and their psychosocial and physical QoL have been impaired by the pandemic. Further, it was found that mental health-related problems such as irritability, attention problems, hyperactivity/impulsivity, depression, anxiety, and OCD symptoms increased in young people compared with the pre-pandemic period. The perceived general and psychosocial QoL during the pandemic, which was lower than before, were highly correlated with these increased mental health-related problems. The physical QoL was also found to have similar but weaker relationships. The findings of our study indicate that the COVID-19 pandemic and associated events such as quarantine, curfew, and school closures have a negative impact on the mental health and QoL of adolescents in Turkey.

There are some points in this study that we think are critical. First all, the research has focused especially on the adolescent age group. The pandemic may have varying levels of effects on different age groups, especially in adolescence, which is a vulnerable period of life, and should be thoroughly examined in this process. Secondly, the pre-pandemic period was taken as a baseline in the evaluations. In this way, the situation during the pandemic was compared with the pre-pandemic period, which was evaluated retrospectively, and particularly the effects of the pandemic process were tried revealed. Thirdly, as mentioned above, due to the variability in the reactions of different countries to the pandemic, we think that this study is important in terms of revealing the results of the relatively strict measures taken in Turkey on adolescents (especially for citizens under the age of 20). Fourth, we tried

Table 2. Comparison of psychosocial symptoms' and Quality of life scores between the pre-pandemic and the pandemic period

	Pre-pandemic period		Pandemic period			
	Mean	SD	Mean	SD	Z	p
Irritability	2.43	±2.51	3.95	±3.2	-6.285	<0.001
Turgay ADHD						
Attention problems	4.92	±5.05	7.18	±5.94	-6.339	<0.001
Hyperactivity and impulsivity	5.14	±4.85	6.33	±5.41	-4.245	<0.001
RCADS-parent report						
Depression	52.2	±12.2	58.5	±14.4	-6.705	<0.001
Separation anxiety	51.3	±10.8	53.6	±12.1	-3.736	<0.001
Generalized anxiety	51.9	±12.1	55.4	±13.6	-5.833	<0.001
Panic	51.4	±12.3	54.4	±13.4	-4.833	<0.001
Social anxiety	48.8	±11.5	51.8	±12.4	-5.198	<0.001
OCD	54.7	±10.4	57.8	±12.0	-5.691	<0.001
Total anxiety	51.9	±12.4	55.5	±13.7	-6.413	<0.001
Total anxiety & depression	52.0	±12.5	56.5	±13.9	-6.829	<0.001
Quality of life (QoL)						
Psychosocial QoL	76.9	±16.2	70.0	±17.7	-6.944	<0.001
Physical health QoL	73.2	±17.5	68.2	±18.5	-4.453	<0.001
Total QoL	75.6	±13.4	69.4	±15.6	-7.084	<0.001

SD: Standard deviation, ADHD: Attention deficit hyperactivity disorder, RCADS: Revised children anxiety and depression scales, OCD: Obsessive-compulsive disorder

evaluating the symptoms related to mental health in a wide spectrum with various scales and evaluated their effects on functioning in relation to the QoL.

In our study, we found a significant increase in attention problems, hyperactivity/impulsivity, and irritability in adolescents compared with the pre-pandemic period. Irritability is characterized by constant anger, negative emotions, and outbursts or tantrums (22), and is included in diagnostic classifications as a symptom of many psychiatric disorders (23). In a systematic review investigating the effects of measures taken due to COVID-19 on child and adolescent mental health (24), irritability in children and adolescents ranged from 16.7% (25) to 73.2% (26). In line with our findings, in an online survey conducted in the early stages of the pandemic, in which 320 children and adolescents aged 3-18 participated, it was shown that distraction (32%) and irritability (31%) were among the most common psychological and behavioral problems (4). In a survey study involving parents of children aged 3-18 in Italy and Spain, it was reported that difficulty in concentrating (76.6%), boredom (52%), irritability (39%), and restlessness (38.8%) were among the common symptoms (27). Additionally, in children with ADHD, symptoms worsen during this period (28), as well as an increase in attention problems has been detected in studies conducted with healthy children (29). In the contrast, some studies showed that there was no significant increase in stress and a decrease in irritability during the pandemic compared to the pre-pandemic period (30). This result was thought to be related to the fact that the study was conducted in the early phase of the pandemic. Additionally, the closure of schools and the decrease in social contact were thought to play a role in the formation of these results, as they reduce the two most important triggers of stress and irritability in adolescents. We interpreted this contradiction as the complexity of adolescence experiences and the variability of the consequences of stressful events depending on cultural contexts.

In our study, it was found that the anxiety and depressive symptoms of adolescents increased compared with the pre-pandemic period. Our result is consistent with the work done so far in this area. There are many studies showing an increase in symptoms associated with anxiety and depression during the COVID-19 pandemic (31). Our finding that OCD-related complaints increase in adolescents is also in line with studies on this subject. Studies argue that

Table 3. Correlations between quality of life scores and psychosocial symptom scores

		Psychosocial QoL	Physical health QoL	Total QoL
Irritability	r	-0.438	-0.262	-0.443
	p	<0.001	0.004	<0.001
Attention problems	r	-0.519	-0.327	-0.532
	p	<0.001	<0.001	<0.001
Hyperactivity and impulsivity	r	-0.287	-0.227	-0.342
	p	0.002	0.014	<0.001
Depression	r	-0.675	-0.311	-0.621
	p	<0.001	0.001	<0.001
Separation anxiety	r	-0.470	-0.244	-0.454
	p	<0.001	0.008	<0.001
Generalized anxiety	r	-0.557	-0.176	-0.487
	p	<0.001	0.057	<0.001
Panic	r	-0.529	-0.236	-0.484
	p	<0.001	0.010	<0.001
Social anxiety	r	-0.659	-0.234	-0.592
	p	<0.001	0.011	<0.001
OCD	r	-0.554	-0.233	-0.511
	p	<0.001	0.011	<0.001
Total anxiety & depression	r	-0.702	-0.283	-0.637
	p	<0.001	0.002	<0.001

OCD: Obsessive-compulsive disorder, QoL: Quality of life

OCD-related problems are a problem that people are most affected in terms of mental health during the pandemic process (32). However, as mentioned above, the mental health consequences of the pandemic may differ among cultures and societies. Besides, the developmental period is also a substantial factor in this respect. Therefore, our study is important because it focuses on the situation of adolescents in Turkey. Moreover, our study addressed the subtypes of anxiety disorders and showed that the problems increased in most types of anxiety.

Considering the QoL, the results of our study showed that after the pandemic, both the total score and the psychosocial and physical health QoL sub-scores decreased in adolescents. Further, in the correlation analysis, psychosocial QoL score was highly negatively correlated with irritability, attention problems, hyperactivity/impulsivity, depression, anxiety, and OCD symptoms. This finding is important in that the increase in mental health-related problems indicates the deterioration of psychosocial functionality. Additionally, this result can be considered an expected natural relationship, but interestingly, correlation analyses revealed that mental health-related problems were associated with the physical health QoL sub-score, albeit weakly. Studies have also reported that children and adolescents have a lower health-related QoL and higher levels of depression and anxiety compared to the pre-pandemic period (33). In a systematic review of six studies (14), three studies reported a decrease in health-related QoL in children and adolescents with the pandemic, two reported no significant change, and one study failed to make a statistical comparison. In this review, the decline in health-related QoL was attributed to the restrictions and practices that adolescents find difficult to comply with, such as quarantine, social isolation, and confinement, as well as deterioration in mental health. The results of our study also seem to be compatible with the results of this review.

The nationwide COPSY ('Corona und Psyche') study conducted in Germany investigated the mental health and health-related QoL of children and adolescents after the first and second waves of COVID. Results, although more modest in the second wave, showed a significant decline in health-related QoL (34,35). Again, in a study evaluating mental

health and health-related QoL in adolescents after the third wave in Germany, the results were found to be similar to those before the pandemic. It has been suggested that this result is related to stress adaptation processes, development of coping strategies, better management of the pandemic, and reduction of quarantine measures and vaccines (36). This study is important in terms of demonstrating that the effects of the pandemic on the QoL can be reversible and may change with the measures taken. However, considering that our study shows the situation of the young people in Turkey in May-June 2021 when the third wave of the pandemic was effective, it does not coincide with the results of the third wave from these studies in Germany. This difference has been interpreted because of the differences in the measures taken between the two countries. The data of our study were collected in May-June 2021. The first wave of the pandemic in Turkey was in the spring of 2020, the second wave was in the winter of the same year; the third wave was seen in the spring of 2021.

As in the whole world, measures have been taken to control the spread of COVID-19 in Turkey. However, the measures seem to contribute to the negative results on mental health and the QoL of adolescents in Turkey. One of these measures, which continued for a very long time, was the curfew for young people under the age of 20. We speculate that one of the possible interpretations of these results is that adolescents staying online for too long may have contributed to these results. While young people stayed at home, many daily activities such as education, socializing and leisure activities were carried out using the internet. This means they are exposed to more online activities than before (37). Additionally, the results can be attributed to factors such as decreased social interaction with peers, decreased contact with support factors, social isolation, perceived stress level by parents, and decreased access to mental health services (38,39).

This study has several limitations. First all, the study was planned as cross-sectional and baseline data were collected retrospectively from the participants. This may have led to possible biases. Second, the study had a modest sample size. Another limitation was that the evaluation relied on self- and parent reports rather than clinician interviews. Requiring participants to remember their pre-pandemic situation retrospectively may be another limitation that increases the possibility of bias in the data. Additionally, the study was applied as an online survey. Online surveys often carry biases, such as content bias affecting the representativeness of the research sample, and social desirability bias, that may be common because of self-report.

CONCLUSION

We conclude that adolescents are especially vulnerable to mental health problems in a pandemic and under the measures implemented to avoid an outbreak. The study indicates that the QoL of adolescents has been impaired by the pandemic in Turkey. Further, it was found that mental health-related problems such as irritability, attention problems, hyperactivity/impulsivity, depression, anxiety, and OCD symptoms increased in young people compared with the pre-pandemic period. Also, results imply an association between QoL and mental health-related problems. In the results of this study, only associations between the pandemic, and deterioration in adolescents' mental health and QoL were demonstrated, and no causal relationships could be concluded. The measures implemented by countries in the pandemic and the pandemic itself should be considered a potential risk of adverse events for adolescents. While measures are necessary to overcome outbreaks, it also must be considered that their impact on the mental health conditions of adolescents and identified strategies to combat this secondary damage. Future studies on this subject should examine how these effects of the pandemic have evolved, and the permanence of these findings should be investigated.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital's Local Ethics Board (decision no: 2021-10-03, date: 17.05.2021).

Informed Consent: Written informed consent were obtained.

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

REFERENCES

1. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed 2020;91:157-60.
2. Dickens BL, Koo JR, Wilder-Smith A, Cook AR. Institutional, not home-based, isolation could contain the COVID-19 outbreak. Lancet 2020;395:1541-2.
3. Velavan TP, Meyer CG. The COVID-19 epidemic. Trop Med Int Health 2020;25:278-80.
4. Jiao WY, Wang LN, Liu J, Fang SF, Jiao FY, Pettoello-Mantovani M, et al. Behavioral and Emotional Disorders in Children during the COVID-19 Epidemic. J Pediatr 2020;221:264-6.e1.
5. Waite P, Pearcey S, Burgess L, Sajid E, Klampe M-L, Sargent M, et al. How the COVID-19 pandemic affected young people's mental health and wellbeing in the UK: A qualitative study. 2022.
6. Jones EAK, Mitra AK, Bhuiyan AR. Impact of COVID-19 on Mental Health in Adolescents: A Systematic Review. Int J Environ Res Public Health 2021;18:2470.

7. Gavin B, Lyne J, McNicholas F. Mental health and the COVID-19 pandemic. Ir J Psychol Med 2020;37:156-8.
8. Somerville LH, Jones RM, Casey BJ. A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. Brain Cogn 2010;72:124-33.
9. Magson NR, Freeman JYA, Rapee RM, Richardson CE, Oar EL, Fardouly J. Risk and Protective Factors for Prospective Changes in Adolescent Mental Health during the COVID-19 Pandemic. J Youth Adolesc 2021;50:44-57.
10. Singh S, Roy D, Sinha K, Parveen S, Sharma G, Joshi G. Impact of COVID-19 and lockdown on mental health of children and adolescents: A narrative review with recommendations. Psychiatry Res 2020;293:113429.
11. Deighton J, Lereya ST, Casey P, Patalay P, Humphrey N, Wolpert M. Prevalence of mental health problems in schools: poverty and other risk factors among 28 000 adolescents in England. Br J Psychiatry 2019;215:1-3.
12. Araújo LA, Veloso CF, Souza MC, Azevedo JMC, Tarro G. The potential impact of the COVID-19 pandemic on child growth and development: a systematic review. J Pediatr (Rio J) 2021;97:369-77.
13. Bellis MA, Hughes K, Ford K, Ramos Rodriguez G, Sethi D, Passmore J. Life course health consequences and associated annual costs of adverse childhood experiences across Europe and North America: a systematic review and meta-analysis. Lancet Public Health 2019;4:e517-28.
14. Nobari H, Fashi M, Eskandari A, Villafaina S, Murillo-Garcia Á, Pérez-Gómez J. Effect of COVID-19 on Health-Related Quality of Life in Adolescents and Children: A Systematic Review. Int J Environ Res Public Health 2021;18:4563.
15. Sibley CG, Greaves LM, Satherley N, Wilson MS, Overall NC, Lee CHJ, et al. Effects of the COVID-19 pandemic and nationwide lockdown on trust, attitudes toward government, and well-being. Am Psychol 2020;75:618-30.
16. Hensel L, Witte M, Caria AS, Fetzer T, Fiorin S, Götz FM, et al. Global Behaviors, Perceptions, and the Emergence of Social Norms at the Onset of the COVID-19 Pandemic. J Econ Behav Organ 2022;193:473-96.
17. Aknin LB, Andretti B, Goldszmidt R, Helliwell JF, Petherick A, De Neve JE, et al. Policy stringency and mental health during the COVID-19 pandemic: a longitudinal analysis of data from 15 countries. Lancet Public Health 2022;7:e417-26.
18. Kocael Ö. Irritability in children and adolescents: Turkish validity and reliability study of the affective reactivity index [dissertation]. Unpublished Medicine thesis: Bursa Uludağ University; 2015.
19. Turgay A. Disruptive behavior disorders child and adolescent screening and rating scales for children, adolescents, parents and teachers. West Bloomfield (Michigan): Integrative Therapy Institute Publication. 1994.
20. Gormez V, Kilincaslan A, Ebesutani C, Orengul AC, Kaya I, Ceri V, et al. Psychometric Properties of the Parent Version of the Revised Child Anxiety and Depression Scale in a Clinical Sample of Turkish Children and Adolescents. Child Psychiatry Hum Dev 2017;48:922-33.
21. Cakin Memik N, Ağaoğlu B, Coşkun A, Uneri OS, Karakaya I. Cocuklar Için Yaşam Kalitesi Olçeğinin 13-18 Yaş Ergen Formunun Geçerlik ve Güvenilirliği [The validity and reliability of the Turkish Pediatric Quality of Life Inventory for children 13-18 years old]. Turk Psikiyatri Derg 2007;18:353-63.
22. Brotman MA, Kircanski K, Stringaris A, Pine DS, Leibenluft E. Irritability in Youths: A Translational Model. Am J Psychiatry 2017;174:520-32.
23. Edition F. Diagnostic and statistical manual of mental disorders. Am Psychiatric Assoc 2013;21:591-643.
24. Panchal U, Salazar de Pablo G, Franco M, Moreno C, Parellada M, Arango C, et al. The impact of COVID-19 lockdown on child and adolescent mental health: systematic review. Eur Child Adolesc Psychiatry 2021:1-27.
25. Amorim R, Catarino S, Miragaia P, Ferreras C, Viana V, Guardiano M. The impact of COVID-19 on children with autism spectrum disorder. 2020.
26. Sama BK, Kaur P, Thind PS, Verma MK, Kaur M, Singh DD. Implications of COVID-19-induced nationwide lockdown on children's behaviour in Punjab, India. Child Care Health Dev 2021;47:128-35.
27. Orgilés M, Morales A, Delvecchio E, Mazzeschi C, Espada JP. Immediate Psychological Effects of the COVID-19 Quarantine in Youth From Italy and Spain. Front Psychol 2020;11:579038.
28. Sciberras E, Patel P, Stokes MA, Coghill D, Middeldorp CM, Bellgrove MA, et al. Physical Health, Media Use, and Mental Health in Children and Adolescents With ADHD During the COVID-19 Pandemic in Australia. J Atten Disord 2022;26:549-62.
29. Cost KT, Crosbie J, Anagnostou E, Birken CS, Charach A, Monga S, et al. Mostly worse, occasionally better: impact of COVID-19 pandemic on the mental health of Canadian children and adolescents. Eur Child Adolesc Psychiatry 2022;31:671-84.
30. Janssens JJ, Achterhof R, Lafit G, Bamps E, Hagemann N, Hiekkaranta AP, et al. The Impact of COVID-19 on Adolescents' Daily Lives: The Role of Parent-Child Relationship Quality. J Res Adolesc 2021;31:623-44.
31. Racine N, McArthur BA, Cooke JE, Eirich R, Zhu J, Madigan S. Global Prevalence of Depressive and Anxiety Symptoms in Children and Adolescents During COVID-19: A Meta-analysis. JAMA Pediatr 2021;175:1142-50.
32. Linde ES, Varga TV, Clotworthy A. Obsessive-Compulsive Disorder During the COVID-19 Pandemic-A Systematic Review. Front Psychiatry 2022;13:806872.
33. Ravens-Sieberer U, Kaman A, Erhart M, Devine J, Schlack R, Otto C. Impact of the COVID-19 pandemic on quality of life and mental health in children and adolescents in Germany. Eur Child Adolesc Psychiatry 2022;31:879-89.
34. Ravens-Sieberer U, Kaman A, Erhart M, Otto C, Devine J, Löffler C, et al. Quality of life and mental health in children and adolescents during the first year of the COVID-19 pandemic: results of a two-wave nationwide population-based study. Eur Child Adolesc Psychiatry 2021:1-14.
35. Ravens-Sieberer U, Kaman A, Otto C, Adedeji A, Napp AK, Becker M, et al. Seelische Gesundheit und psychische Belastungen von Kindern und Jugendlichen in der ersten Welle der COVID-19-Pandemie – Ergebnisse der COPSY-Studie [Mental health and psychological burden of children and adolescents during the first wave of the COVID-19 pandemic-results of the COPSY study]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2021;64:1512-21.
36. Hussong J, Möhler E, Kühn A, Wenning M, Gehrke T, Burckhart H, et al. Mental Health and Health-Related Quality of Life in German Adolescents after the Third Wave of the COVID-19 Pandemic. Children (Basel) 2022;9:780.
37. Chen IH, Chen CY, Pakpour AH, Griffiths MD, Lin CY. Internet-Related Behaviors and Psychological Distress Among Schoolchildren During COVID-19 School Suspension. J Am Acad Child Adolesc Psychiatry 2020;59:1099-102.e1.
38. Masonbrink AR, Hurley E. Advocating for Children During the COVID-19 School Closures. Pediatrics 2020;146:e20201440.
39. Brown SM, Doom JR, Lechuga-Peña S, Watamura SE, Koppels T. Stress and parenting during the global COVID-19 pandemic. Child Abuse Negl 2020;110:104699.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:356-363
DOI: 10.4274/BMJ.galenos.2022.2022.7-4

Research

The Relationship Between Blood Transfusions and Mortality and Length of Stay in Patients Followed up with a Diagnosis of COVID-19 in Intensive Care Units

COVID-19 Tanısıyla Yoğun Bakım Ünitelerinde Takipli Hastalarda Kan Transfüzyonlarının Mortalite ve Yoğun Bakımda Kalış Süreleri ile İlişkisi

Gülsen Keskin, Melis Sumak Hazır, Dilek Ünal, Jülide Ergil

University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Ankara, Turkey

ABSTRACT

Objective: The number of studies investigating the requirement for red blood cell (RBC) transfusions and the effects of transfusions on mortality in intensive care unit (ICU) patients with coronavirus disease-2019 (COVID-19) is limited. This study investigated the relationship between RBC transfusions and the prognostic laboratory criteria of COVID-19, ICU length of stay, and mortality in ICU patients with a diagnosis COVID-19.

Methods: This retrospective study included 401 patients aged 18 years and older who were followed up and treated in the ICU with a positive real-time polymerase chain reaction test result for COVID-19 between September 01, 2020 and January 31, 2021. After obtaining the ethics committee approval, the demographic data, clinical data, and laboratory results of the patients included in the study were screened from the electronic medical record system and recorded in data-recording forms.

Results: The mean age of the 393 patients included in the analyses was 69.42±12.90 years, and 52.7% were male. Eighty-eight percent (n=346) of the patients had comorbidities, with 35.9% having three or more comorbidities. Forty (10.2%) patients who received transfusion had higher values of Acute Physiology and Chronic Health Evaluation score ($p<0.05$), ICU length of stay ($p<0.001$), D-dimer ($p<0.05$), brain natriuretic peptide ($p=0.001$), lactate dehydrogenase (LDH) ($p<0.05$), and creatinine ($p=0.001$) than those without transfusion. The lowest hemoglobin value ($p<0.001$) and LDH value ($p<0.05$) were found to be factors effective in transfusion status. The mortality rate was higher in patients who required RBC transfusions (72.5%) than in patients without transfusion requirements (45.9%) ($p=0.001$). The rate of having three or more diseases was higher in patients with transfusions (55.0%) than in patients without transfusions (33.7%) ($p<0.05$).

Conclusion: This retrospective study demonstrated the association of RBC transfusions with an increase in ICU length of stay and mortality. The decision of transfusion for the critically ill group followed up in the COVID-19 ICU should be individualized, and unnecessary transfusions should be avoided.

Keywords: COVID-19, mortality, transfusion, intensive care

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVID-19) nedeniyle yoğun bakım ünitelerinde (YBÜ) takip edilen hastalarda eritrosit süspansiyonu (ES) transfüzyonu ihtiyacı ve transfüzyonların mortalite üzerine etkilerini araştıran çalışmalar yetersizdir. Bu çalışmada, yoğun bakımlarda COVID-19 tanısı ile takip edilen hastalarda ES transfüzyonlarının COVID-19 prognostik laboratuvar kriterleri YBÜ'de kalış süreleri ve mortalite ile ilişkisinin araştırılması amaçlandı.

Gereç ve Yöntem: Retrospektif olarak planlanan bu çalışmaya 01.09.2020-31.01.2021 tarihleri arasında, YBÜ'de takip ve tedavi edilen 18 yaş ve üzeri, gerçek zamanlı polimeraz zincir reaksiyonu testi pozitif olan 401 hasta alındı. Etik kurul onayı sonrasında, dahil edilen hastaların demografik verileri, klinik verileri ve laboratuvar sonuçları elektronik tıbbi kayıt sisteminden hasta kayıtları taranarak veri kayıt formları doldurulduu.

Address for Correspondence: Gülsen Keskin, University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Ankara, Turkey

Phone: +90 533 413 35 24 E-mail: drgulsenkeskin@gmail.com ORCID ID: orcid.org/0000-0002-9990-5533

Cite as: Keskin G, Sumak Hazır M, Ünal D, Ergil J. The Relationship Between Blood Transfusions and Mortality and Length of Stay in Patients Followed up with a Diagnosis of COVID-19 in Intensive Care Units. Med J Bakirkoy 2022;18:356-363

Presented in: This study was presented as an oral presentation at the 25th Uludag Winter Symposium on February 25-26, 2022.

Received: 20.07.2022
Accepted: 21.09.2022

Bulgular: Analizlere dahil edilen 393 hastanın %52,7'i erkek, hastaların yaş ortalaması 69,42±12,90 idi. Hastaların %88'inin (346) yandaş hastalığı vardı ve bunların %35,9'unda 3 ve üzeri ek hastalık saptandı. Transfüzyon yapılan 40 (%10,2) hastanın Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi skoru (p<0,05), yoğun bakımda kalış süresi (p<0,001), D-dimer (p<0,05), beyin kaynaklı natriüretik peptid (p=0,001), laktat dehidrogenaz (LDH) (p<0,05) ve kreatinin (p=0,001) değeri transfüzyon yapılmayan hastalara göre yüksek bulundu. En düşük hemoglobin değeri (p<0,001) ve LDH değeri (p<0,05) transfüzyon yapılma durumu üzerinde etkili faktörler olarak saptandı. ES transfüzyonu yapılan hastalardaki ölüm oranı (%72,5), transfüzyon yapılmayan hastalardakine göre (%45,9) daha yüksek bulundu (p=0,001). Transfüzyon yapılan hastalardaki 3 ve üzeri hastalığa sahip olma oranı (%55,0), transfüzyon yapılmayan hastalara göre (%33,7) daha yüksek bulundu (p<0,05).

Sonuç: Bu retrospektif çalışma sonucunda ES transfüzyonlarının artmış YBÜ kalış süresi ve mortalite ile ilişkisi gösterilmiştir. COVID-19 YBÜ'de takip edilen kritik hasta grubunda transfüzyon kararının hasta düzeyinde özelleştirilmesi ve gereksiz transfüzyonlardan kaçınılması gerektiği her zaman göz önünde bulundurulmalıdır.

Anahtar Kelimeler: COVID-19, mortalite, transfüzyon, yoğun bakım

INTRODUCTION

Many patients diagnosed with coronavirus disease-2019 (COVID-19) pneumonia caused by severe acute respiratory syndrome coronavirus-2 are followed up in intensive care units (ICU). Studies have reported a higher mortality rate in the advanced age group with comorbidities (1).

ICU patients require blood component transfusions due to both COVID-19-related complications and comorbidities (2). Anemia is the most common reason for red blood cell (RBC) transfusion requirements among ICU patients. Anemia is common in ICU patients as an iatrogenic-induced condition due to chronic disease, iron deficiency, and repetitive sampling (2). Although the transfusion rate has been reported as 38.3% in non-COVID-19 patients in ICUs (3), a recent study found a RBC transfusion rate of 41.01% in COVID-19 patients in ICUs and associated this with increased mortality (4).

Blood transfusions have been shown to be associated with morbidity and mortality, such as prolonged length of hospital and ICU stay, the requirement for mechanical ventilation, and multiorgan failure (5). Prolonged ICU length of stay (LOS) causes both an increase in the cost of healthcare services and the inability of patients with an ICU requirement to receive appropriate healthcare (6).

Despite the published guidelines on blood transfusions, the decision of patient blood management is currently left to the clinician, and there is no consensus among clinicians in this respect (7,8). Moreover, the number of studies investigating the relationship between blood transfusions and other laboratory parameters with ICU LOS and mortality in patients with COVID-19 in the ICU is limited. A better understanding of the factors associated with mortality may allow for better management of these patients (9).

Therefore, we investigated the effects of RBC transfusions on ICU LOS and mortality in ICU patients with COVID-19.

METHODS

The study was approved by the University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (decision no: 109/14, date: 19.04.2021). We retrospectively evaluated the records of patients aged 18 years and older who were followed up in the level 3 COVID-19 ICU affiliated with the anesthesiology and reanimation clinic between September 01, 2020 and January 31, 2021, and who had a positive COVID-19 reverse transcriptase-polymerase chain reaction test result.

Demographic data, clinical data, and laboratory data (complete blood count, coagulation parameters, inflammatory parameters) of the patients included in the study were screened from an electronic medical record system and recorded in data-recording forms. Hypertension (HT), cardiovascular disease (CVD), chronic obstructive pulmonary disease, chronic kidney disease (CKD), cerebrovascular disease, diabetes mellitus, and cancer were noted as comorbidities. Blood and blood product transfusions, Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores, drugs used [steroid, low-molecular-weight heparin (LMWH), acetylsalicylic acid (ASA)], length of intensive care and hospital stay, and discharge status (discharged to the ward/exitus) of the patients were recorded.

Statistical Analysis

We calculated the descriptive properties of the variables (mean, median, number, and percentage). Numerical variables were checked to determine whether they followed a normal distribution. In two-group comparisons, the Student's t-test was used for normally distributed numerical variables, while the Mann-Whitney U test was used for non-normally distributed numerical variables. The comparison of categorical variables was performed using the chi-square test. We performed univariate logistic regression while conducting a risk factor analysis for mortality. This was followed by a multivariate logistic regression test by adding all variables. A p-value of <0.05 was considered significant. The Statistical Package for the Social Sciences version 17 (Chicago, USA) software was used to evaluate the results.

RESULTS

The study included 401 patients. Two patients were excluded from the study for treatment refusal, two patients who was referred to another hospital, one patient for being transferred to the non-COVID-19 ICU, two patients who received only fresh frozen plasma transfusions, and one patient who received only platelet transfusions. Statistical analysis was performed on 393 patients.

The median age of the 393 patients included in the analysis was 71 [minimum (min)-maximum (max): 19-95] years, and 52.7% of the patients were male and 47.3% were female. Of these patients, 346 (88.0%) had comorbidities. Of those with comorbidities, 64.7% had two or more comorbidities. The median APACHE-II score was 15 (min-max: 1-41). The number of patients who received RBC transfusions was 40 (10.2%). The median ICU LOS was 7 (min-max: 1-49) days. The number of patients transferred to the ward was 200 (50.9%), and the number of patients who died was 193 (49.1%) (Table 1).

The mean age, male-to-female ratios, APACHE-II scores, and drug use (steroid, LMWH, ASA), transfusion rates, and transfusion status were statistically similar ($p>0.05$). The transfusion group had a higher rate of having three or more diseases than the non-transfusion group ($p<0.008$). Patients with transfusion had higher admission hemoglobin (Hb) and lowest Hb values and longer ICU LOS than those without transfusion ($p<0.001$). Patients who received RBC transfusion had a higher mortality rate than non-transfusion patients ($p<0.003$) (Table 2).

According to multivariate logistic regression analysis, the lowest Hb value and lactate dehydrogenase (LDH) value were factors effective in transfusion status ($p<0.001$; $p<0.020$) (Table 3). The use of antithrombotic agents, a low lowest Hb value, and high brain natriuretic peptide (BNP) levels increased the risk of ICU stay of more than 7 days. A high APACHE-II score was found to be an independent risk factor for a LOS of more than 30 days ($p<0.009$) (Table 4).

ICU LOS, APACHE-II score, LDH, creatinine, international normalized ratio (INR), procalcitonin, thrombocytopenia, and lymphopenia were found to be factors affecting mortality (Table 5).

Table 1. Demographic data and clinical characteristics

Variables	
Age (years), Median (min-max)	71 (19-95)
Gender (female/male) n (%)	186 (47.3)/207 (52.7)
APACHE-II score Median (min-max)	15 (1-41)
ICU length of stay (days) Median (min-max)	7 (1-49)
Transfusion (yes/no) n (%)	40 (10.2)/353 (89.8)
Exitus n (%)	193 (49.1)

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, ICU: Intensive care unit, min-max: Minimum-maximum

DISCUSSION

This retrospective study investigating RBC transfusion and mortality and ICU LOS in ICU patients with COVID-19 revealed an association between RBC transfusions and increased ICU LOS and mortality. The results of this study showed that patients with RBC transfusions had higher D-dimer, BNP, LDH, and creatinine values and that the lowest Hb and LDH values were predictive of transfusion in COVID-19 patients.

Some studies have reported mild anemia in critically ill COVID-19 patients (7). The causes of anemia in COVID-19 patients may include impaired iron metabolism secondary to a cytokine storm, the shortened lifespan of RBCs by inflammation, direct infection of blood cells by the virus, and iatrogenic phlebotomy (2). The analysis of admission Hb values of the patients in this study showed that the values were within the normal range in the non-transfusion group, whereas the mean value was 9.4 g/dL in the transfusion group, which supports the results of mild anemia reported in previous studies. The transfusion rate in our study was 10.2%, which was lower than the 41.9% reported by Grandone et al. (4) in 179 patients followed up in the ICU. Mortality rates in the ICU patients who were transfused were 76.7% in this study and 72.5% in our patient group. Although the studies looked similar in terms of demographic characteristics, the transfusion Hb threshold values, APACHE scores and LOS in the ICU were not reported. The difference in transfusion and mortality rates may be due to our use of restrictive transfusion strategies. Indeed, restrictive transfusion strategies have been shown to significantly reduce patient mortality (2).

As there are no published guidelines on blood transfusions for COVID-19 patients, current guidelines are also used for the decision of transfusion in COVID-19 patients. According to the American Association of Blood Banks blood transfusion guidelines published in 2016, the Hb threshold value for RBC transfusion is 7 g/dL for patients who are not expected to have active bleeding, including critically ill patients (10). However, it is recommended that each patient be evaluated individually during transfusion.

Table 2. Demographic and clinical data of patients with and without transfusion

Variables		Transfusion group n=40	Non-transfusion group n=353	p
Age (years) Median (min-max)		72.00 (44.00-92.00)	71.00 (19.00-95.00)	0.215
Gender (M/F), n (%)		17/23 (42.5/57.5)	190/163 (53.8/46.2)	0.174
Comorbidity, n (%)	No comorbidity	2 (5.0)	45 (12.7)	0.008
	≥3 comorbidities	22 (55.0)	119 (33.7)	
Hypertension		29 (72.5)	215 (61.3)	0.22
Diabetes		16 (40)	132 (37.6)	0.90
CKD		11 (27.5)	23 (6.6)	<0.001
Cardiovascular disease		10 (25)	77 (21.9)	0.81
Neurological disease		6 (15)	50 (14.2)	1.00
Malignancy		5 (12.5)	21 (6)	0.17
COPD		3 (12)	62 (23.5)	0.28
Others		5 (12.5)	40 (11.4)	0.79
APACHE-II score Median (min-max)		16.00 (7.00-41.00)	11.00 (6.00-6.20)	0.49
Admission Hb (g/dL) Median (min-max)		8.65 (6.00-19.10)	12.30 (7.40-7.20)	<0.001
Lowest Hb (g/dL) Median (min-max)		6.70 (3.90-8.80)	11.00 (6.00-6.20)	<0.001
ΔHb Median (min-max)		2.25 (2.00-3.20)	1.00 (1.35-1.40)	<0.001
ICU length of stay (days) Median (min-max)		11.50 (1.00-37.00)	7.00 (1.00-49.00)	<0.001
Discharge status from ICU n (%)	Exitus	29 (72.5)	164 (46.5)	0.003
	Ward	11 (27.5)	189 (53.5)	
Drug use, n (%)	Steroid	34 (85.0)	322 (91.2)	0.202
	LMWH	38 (95.0)	349 (98.9)	0.117
	ASA	26 (65.0)	234 (66.3)	0.870

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, ICU: Intensive care unit, LMWH: Low-molecular-weight heparin, ASA: Acetylsalicylic acid, ΔHb: Admission Hb value-lowest Hb value, Hb: Hemoglobin, min-max: Minimum-maximum

For the critically ill patient group followed up in the ICU, the Hb value, oxygenation, intravascular volume, and comorbidities play an important role in the decision of blood transfusion (7). Unnecessary transfusion may increase the patient's inflammatory markers, progression in lung damage, deterioration in oxygenation, and coagulopathy, along with transfusion-related complications such as transfusion assosiated circulatory overload and transfusion related lung injury (11,12). To reduce lung damage in COVID-19 patients, the number of transfusions and the number of different donors should be limited, and oxygenation should be improved with non-transfusion methods (7,13).

In the advanced restrictive transfusion approach, the patient's general condition may worsen due to deterioration in the peripheral circulation, impaired oxygenation, and increased cardiac and respiratory workload. Oxygenation, which is impaired secondary to acute respiratory distress syndrome, may become even worse when a very restrictive transfusion approach is preferred in the group of patients with advanced age and comorbidities followed up in the COVID-19 ICU (2).

In our study, the mean threshold value for Hb transfusion was found to be 6.7 g/dL. Among the parameters examined in the data, the lowest Hb level was found to be effective in

Table 3. Factors affecting to RBC transfusion

Variables	OR	95% CI Lower threshold	95% CI Upper threshold	p
Hb (g/dL)	1.040	0.768	1.408	0.799
Lowest Hb (g/dL)	0.074	0.026	0.208	<0.001
ΔHb	0.135	0.072	0.254	<0.001
APACHE-II score	0.968	0.884	1.059	0.474
Length of ICU stay (days)	1.057	0.987	1.132	0.112
D-dimer	0.958	0.818	1.123	0.598
BNP	1.000	1.000	1.000	0.747
LDH	1.002	1.000	1.003	0.024
Creatinine	1.250	0.877	1.781	0.216
Platelet	0.996	0.990	1.002	0.179
2≥ comorbidities	1.298	0.325	5.181	0.712

RBC: Red blood cells, Hb: Hemoglobin, APACHE-II: Acute Physiology and Chronic Health Evaluation-II; BNP: Brain natriuretic peptide, LDH: Lactate dehydrogenase, OR: Odds ratio, CI: Confidence interval, ICU: Intensive care unit

transfusion decisions. Given these observations, we consider that the restrictive blood transfusion approach should be adopted among clinicians in the ICU where the study was conducted in accordance with the guidelines. In this retrospective study, the data on the patients' oxygenation and intravascular volumes could not be evaluated since they were not complete. Moreover, although the lowest Hb value of patients in the ICU affected their transfusion status, we did not find it to be a risk factor for mortality. Therefore, we can speculate that the total effect of comorbid conditions is more important than the effect of isolated anemia and transfusion in terms of prognosis.

Advanced age, smoking, HT, diabetes, CVD, respiratory diseases, kidney disease, and malignancies have been associated with ICU mortality among COVID-19 patients (14). Our study demonstrated that the presence of comorbidities affected the requirement for and decision of transfusion and that the patient population with three or more comorbidities received more RBC transfusions compared with the group without comorbidity. The separate analysis of comorbidities showed that the presence of CKD was higher in the transfusion group.

Routine biochemical, hematological, and immunochemical laboratory tests have been widely used to evaluate disease severity, select appropriate treatments, and monitor treatment responses in COVID-19 patients. Previous studies have reported the prognostic value of increased LDH, D-dimer, and creatinine levels, along with lymphopenia and thrombocytopenia (15). The results of our study revealed that APACHE-II score, ICU LOS, INR, lymphopenia, thrombocytopenia, LDH, and creatinine levels were risk factors for mortality.

Studies have shown an association between advanced age, comorbid diseases, APACHE-II scores, elevated levels of urea and creatinine, and prolonged ICU LOS. Prolonged ICU LOS has not been clearly defined, and different durations (>7, >14, >21, >30 days) have been used depending on subjective evaluations (16-19). Susceptibility to anemia has been reported to be increased by an increased LOS, which is associated with morbidity and mortality. Our study revealed longer LOS and higher mortality rates in the transfusion group compared to the non-transfusion group.

This study investigated transfusion-related mortality and ICU LOS in patients followed up in the COVID-19 ICU, but it has several limitations. First, there was no standardized protocol for transfusion, and only previous transfusions were analyzed in this retrospective study. Because to the lack of data, pre-transfusion oxygenation and intravascular volume could not be evaluated. Additionally, the study included only patients who received RBC transfusions, while other blood component transfusions were excluded due to the limited number of patients.

Based on the results of this study, we suggest that there is a need for multicenter prospective studies with transfusion protocols that also evaluate the oxygenation and intravascular status, as well as the Hb values and comorbid conditions of patients. Moreover, examining large patient populations and transfusions of other non-RBC blood and blood products will also guide clinicians.

Table 4. Multivariate analysis for ICU stay of more than 7 days and more than 30 days

Variables	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Risk analysis for ICU stay of more than 7 days				
Hypertension	1.228 (0.679-2.222)	0.497	-	-
CKD	0.756 (0.206-2.776)	0.010	-	-
APACHE-II score	1.086 (1.020-1.156)	0.010	-	-
Anticoagulants	1.970 (0.121-31.992)	0.634	-	-
Antithrombotics	2.483 (1.306-4.721)	0.006	2.730 (1.843-5.529)	0.005
Admission Hb (g/dL)	1.272 (1.066-1.517)	0.008	-	-
Lowest Hb (g/dL)	1.416 (1.179-1.700)	0.000	1.569 (1.277-1.926)	<0.001
ΔHb	1.218 (0.975-1.522)	0.082	-	-
LDH	1.730 (0.777-3.851)	0.179	-	-
Creatinine	0.710 (0.287-1.757)	0.459	-	-
Ferritin	0.417 (0.162-1.073)	0.070	-	-
BNP	0.619 (0.330-1.164)	0.137	0.378 (0.182-0.786)	0.009
D-dimer	2.004 (0.962-4.177)	0.064	-	-
INR	0.717 (0.377-1.363)	0.310	-	-
Procalcitonin	0.456 (0.196-1.061)	0.068	-	-
PLT	1.217 (0.445-3.324)	0.702	-	-
Lymphocyte	1.107 (0.612-2.004)	0.736	-	-
RBC transfused	3.263 (0.572-18.619)	0.183	-	-
Risk analysis for ICU stay of more than 30 days				
Hypertension	2.741 (0.555-13.540)	0.216	-	-
CKD	6.464 (1.153-36.231)	0.034	-	-
APACHE-II score	1.153 (1.035-1.283)	0.009	1.153 (1.035-1.283)	0.009
Anticoagulants	77750116.39 (0-)	0.999	-	-
Antithrombotics	3.2 (0.391-26.202)	0.278	-	-
Admission Hb (g/dL)	1.046 (0.721-1.517)	0.814	-	-
Lowest Hb (g/dL)	0.826 (0.603-1.132)	0.234	-	-
ΔHb	1.408 (0.977-2.030)	0.067	-	-
LDH	90870450.6 (0-)	0.998	-	-
Creatinine	2.414 (0.469-12.426)	0.292	-	-
Ferritin	92020777.43 (0-)	0.998	-	-
BNP	0 (0-)	0.997	-	-
D-dimer	1.818 (0.22-15.012)	0.579	-	-
INR	0 (0-)	0.997	-	-
Procalcitonin	1.947 (0.236-16.057)	0.536	-	-
Platelet	0 (0-)	0.998	-	-
Lymphocyte	0.979 (0.255-3.759)	0.975	-	-
RBC transfused	0 (0-)	0.998	-	-

CKD: Chronic kidney disease, ICU: Intensive care unit, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, ΔHb: Admission Hb value-lowest Hb value, LDH: Lactate dehydrogenase, BNP: Brain natriuretic peptide, INR: International normalized ratio, RBC: Red blood cell, PLT: Platelet, OR: Odds ratio, CI: Confidence interval, Hb: Hemoglobin

Table 5. Analysis of risk factors for mortality

Variables	Univariate				Multivariate			
	OR	CI		p	OR	CI		p
>70 years	1.744	1.166	2.607	0.007	-	-	-	-
Hypertension	1.589	1.052	2.402	0.028	-	-	-	-
CKD	2.670	1.241	5.745	0.012	-	-	-	-
Duration of ICU	0.946	0.918	0.975	0.000	0.955	0.921	0.991	0.014
APACHE-II score	1.149	1.104	1.196	0.000	1.095	1.042	1.151	0.000
Anticoagulants	0.384	0.074	2.002	0.256	-	-	-	-
Antithrombotics	0.555	0.364	0.847	0.006	-	-	-	-
Admission Hb (g/dL)	0.916	0.833	1.007	0.068	-	-	-	-
Lowest Hb (g/dL)	0.921	0.841	1.009	0.076	-	-	-	-
ΔHb	1.002	0.886	1.133	0.978	-	-	-	-
LDH	10.868	3.252	36.322	0.000	9.961	2.425	40.908	0.001
Creatinine	10.602	6.260	17.957	0.000	4.650	2.482	8.712	0.000
Ferritin	2.800	1.392	5.631	0.004	-	-	-	-
BNP	4.682	3.049	7.192	0.000	-	-	-	-
D-dimer	4.067	1.956	8.454	0.000	-	-	-	-
INR	2.408	1.584	3.660	0.000	1.786	1.026	3.108	0.040
Procalcitonin	22.68	5.388	95.476	0.000	9.298	2.074	41.677	0.004
Platelet	3.458	1.977	6.047	0.000	2.570	1.184	5.579	0.017
Lymphocyte	3.914	2.537	6.038	0.000	3.493	1.997	6.110	0.000

CKD: Chronic kidney disease, ICU: Intensive care unit, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, ΔHb: Admission Hb value-lowest Hb value, LDH: Lactate dehydrogenase, BNP: Brain natriuretic peptide, INR: International normalized ratio, Hb: Hemoglobin, OR: Odds ratio, CI: Confidence interval

CONCLUSION

The results of this retrospective study investigating the effects of RBC transfusions in the COVID-19 ICU on mortality and ICU LOS showed an association between RBC transfusions and prolonged ICU LOS and increased mortality in ICU patients with COVID-19. The results also revealed that the admission Hb level affected transfusion decisions in ICU patients, but it had no effect on mortality. This study demonstrated that the transfusion decisions of ICU patients should be individualized, and unnecessary transfusions should be avoided.

ETHICS

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (decision no: 109/14, date: 19.04.2021).

Informed Consent: Retrospective study.

Authorship Contributions

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

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

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

REFERENCES

1. Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. Anaesthesia 2020;75:1340-9.
2. Beverina I, Borotto E, Novelli C, Radrizzani D, Brando B. Iatrogenic anaemia and transfusion thresholds in ICU patients with COVID-19 disease at a tertiary care hospital. Transfus Apher Sci 2021;60:103068.
3. Shehata N, Forster AJ, Lawrence N, Ducharme R, Fergusson DA, Chassé M, et al. Transfusion Patterns in All Patients Admitted

to the Intensive Care Unit and in Those Who Die in Hospital: A Descriptive Analysis. PLoS One 2015;10:e0138427.

4. Grandone E, Pesavento R, Tiscia G, De Laurenzo A, Ceccato D, Sartori MT, et al. Mortality and Transfusion Requirements in COVID-19 Hospitalized Italian Patients According to Severity of the Disease. J Clin Med 2021;10:242.
5. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, et al. Anemia and blood transfusion in critically ill patients. JAMA 2002;288:1499-507.
6. Kıray G, İnal MT, Memiş D, Turan FN. Investigation of the Factors Affecting Prolonged Intensive Care Unit. Turk J Intensive Care 2020;18:84-90.
7. Baron DM, Franchini M, Goobie SM, Javidroozi M, Klein AA, Lasocki S, et al. Patient blood management during the COVID-19 pandemic: a narrative review. Anaesthesia 2020;75:1105-13.
8. Fan BE, Ong KH, Chan SSW, Young BE, Chong VCL, Chen SPC, et al. Blood and blood product use during COVID-19 infection. Am J Hematol 2020;95:E158-60.
9. Taylor EH, Hofmeyr R, Torborg A, Tonder CV, Boden R, Earle E, et al. Risk factors and interventions associated with mortality or survival in adult COVID-19 patients admitted to critical care: a systematic review and meta-analysis. South Afr J Anaesth Analg 2020;26:116-27.
10. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA 2016;316:2025-35.
11. Vlaar APJ, Toy P, Fung M, Looney MR, Juffermans NP, Bux J, et al. A consensus redefinition of transfusion-related acute lung injury. Transfusion 2019;59:2465-76.
12. Yoshida T, Prudent M, D'alessandro A. Red blood cell storage lesion: causes and potential clinical consequences. Blood Transfus 2019;17:27-52.
13. Vincent JL, Jaschinski U, Wittebole X, Lefrant JY, Jakob SM, Almekhlafi GA, et al. Worldwide audit of blood transfusion practice in critically ill patients. Crit Care 2018;22:102.
14. Martin CM, Hill AD, Burns K, Chen LM. Characteristics and outcomes for critically ill patients with prolonged intensive care unit stays. Crit Care Med 2005;33:1922-7; quiz 1936.
15. Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. Clin Chim Acta 2020;510:475-82.
16. Zampieri FG, Ladeira JP, Park M, Haib D, Pastore CL, Santoro CM, et al. Admission factors associated with prolonged (>14 days) intensive care unit stay. J Crit Care 2014;29:60-5.
17. Chalfin DB. Length of intensive care unit stay and patient outcome: the long and short of it all. Crit Care Med 2005;33:2119-20.
18. Çevik B, Geyik FD. Prolonged Stay in Intensive Care Unit: Retrospective Analysis of Predisposing Factors and Outcome. Turk J Intens Care 2019;17:96-101.
19. Oliveira AB, Dias OM, Mello MM, Araújo S, Dragosavac D, Nucci A, et al. Factors associated with increased mortality and prolonged length of stay in an adult intensive care unit. Rev Bras Ter Intensiva 2010;22:250-6.

Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:364-369
DOI: 10.4274/BMJ.galenos.2022.2022.9-3

Research

The Predictive Value of Systemic Immune Inflammation Index in Patients Hospitalized in the Intensive Care Unit

Yoğun Bakım Ünitesinde Yatan Hastalarda Sistemik İmmün Enflamasyon İndeksinin Prediktif Değeri

Habip Yılmaz[1], Cemal Kazezoğlu[2], Asuman Gedikbaşı[3]

[1]University of Health Sciences Turkey, İstanbul Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey
[2]University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Biochemistry, İstanbul, Turkey
[3]İstanbul University Institute of Child Health, Department of Pediatric Basic Sciences, İstanbul, Turkey

ABSTRACT

Objective: The systemic immune-inflammation index (SII), predicated on peripheral platelet, neutrophil, and lymphocyte counts, has been shown to be an effective predictive tool in different illnesses. We examined the role of the baseline SII in predicting short-term outcomes in patients hospitalized in the intensive care unit (ICU).

Methods: The data of patients followed in the ICU between January 01, 2019 and December 31, 2019, were included in the study. Demographic data, the length of stay in the ICU, additional diseases, Acute Physiology and Chronic Health Evaluation-II score, presence of comorbidity and mortality, and complete blood count test results were recorded from electronic files. The SII was calculated as platelet × neutrophil/lymphocyte counts. The predictive value of SII on the clinical outcomes (length of stay, and 30-day mortality) were investigated retrospectively.

Results: Based on the inclusion and exclusion criteria, 201 patients (104 female and 97 male) were selected to be included. The median age [interquartile range (IQR): 61-82] was 73. The median length of stay in the hospital was 19 days (IQR: 8-32). Fifty-nine (n=59) patients (29.3%) died, leaving 142 patients (70.64%) who were discharged alive. Non-survivors had significantly higher SII values, (median; 1,566; IQR: 812-3,455 vs. 1,019; IQR 599-1,771, p=0.037) compared to survivors. The hazard ratio (95% confidence interval) for the high-SII group compared with the low-SII group for 30-day all-cause mortality was 2.61 (1.33-4.79), and 1.23 (0.71-2.61) respectively.

Conclusion: In ICU patients, a high SII was linked to higher mortality. Consequently, SII is a predictive biomarker of patients that may be valuable. Additional research should be conducted to assess our findings using prospective trials with longer follow-ups.

Keywords: Systemic immune inflammation index, intensive care, predictivity

ÖZ

Amaç: Periferik kanda, trombosit, nötrofil ve lenfosit sayılarına dayanan sistemik immün-enflamasyon indeksinin (SII) farklı hastalıklarda etkili bir öngörü aracı olduğu gösterilmiştir. Bu çalışmanın amacı, yoğun bakım ünitesinde (YBÜ) yatan hastalarda kısa dönem sonuçları tahmin etmede başlangıç SII'nin rolünü araştırmaktır.

Gereç ve Yöntem: 01 Ocak ile 31 Aralık 2019 tarihleri arasında YBÜ'de izlenen hastaların verileri çalışmaya dahil edildi. Demografik veriler, YBÜ'de kalış süresi, ek hastalıklar, Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II skoru, komorbidite ve mortalite varlığı ve tam kan sayımı test sonuçları elektronik dosyalardan kaydedildi. SII, trombosit x nötrofil/lenfosit sayıları olarak hesaplandı. SII'nin klinik sonuçlar (kalış süresi ve 30 günlük mortalite) üzerindeki prediktif değeri geriye dönük olarak araştırıldı.

Bulgular: Dahil etme ve hariç tutma kriterlerine göre, dahil edilmek üzere toplam 201 hasta (104 kadın ve 97 erkek) seçildi. Medyan yaş 73 [çeyrekler açıklığı (IQR): 61-82] bulundu. Hastanede ortalama kalış süresi 19 gündü (IQR: 8-32). Elli dokuz (n=59) hasta (%29,3) öldü, 142 hasta (%70,64) sağ olarak taburcu edildi. Ölen hastalar, hayatta kalanlara kıyasla önemli ölçüde daha yüksek SII değerlerine sahipti (medyan; 1.566; IQR: 812-3.455 ve 1.019; IQR 599-1771, p=0,037). Otuz günlük tüm nedenlere bağlı ölüm için düşük SII grubuna kıyasla yüksek SII grubu için risk oranı (%95 güven aralığı) sırasıyla 2,61 (1,33-4,79) ve 1,23 (0,71-2,61) idi.

Address for Correspondence: Asuman Gedikbaşı, İstanbul University Institute of Child Health, Department of Pediatric Basic Sciences, İstanbul, Turkey
Phone: +90 212 414 20 00/31553 E-mail: asugedikbasi@yahoo.com ORCID ID: orcid.org/0000-0001-7121-6077

Cite as: Yılmaz H, Kazezoğlu C, Gedikbaşı A. The Predictive Value of Systemic Immune Inflammation Index in Patients Hospitalized in the Intensive Care Unit. Med J Bakirkoy 2022;18:364-369

Received: 13.09.2022
Accepted: 16.09.2022

Sonuç: YBÜ hastalarında yüksek SII, daha yüksek mortalite ile bağlantılıydı. Sonuç olarak, SII, yoğun bakım hastalarının sonuçları için öngörücü bir biyobelirteç olabilir. Ancak, bulgularımızı doğrulamak için daha uzun takip süreli, prospektif ek araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: Sistemik immün enflamasyon indeksi, yoğun bakım, prediktivite

INTRODUCTION

In systemic inflammation, changes in peripheral blood such as neutrophilia, lymphopenia and thrombocytosis are observed (1). In the last decade, new biomarkers that can be easily calculated using complete blood count (CBC) parameters have been used in the determination of systemic inflammation. The indices obtained with the ratios of hematological parameters in the CBC test are accepted as a good indicator of the systemic inflammatory response, and are suggested as biomarkers to support in the identification, monitoring, and risk assessment of many diseases (2-5). The severity and mortality of various inflammatory conditions especially cancer have been predicted using hematological inflammation indices, such as the neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio, platelet/lymphocyte ratio (PLR) (6-8). Systemic inflammation index (SII) was first described as a promising tool for determining hepatocellular carcinoma (HCC) treatment strategy and a powerful prognostic indicator of poor outcome in patients with HCC (9). It has been proposed as a potent predictive tool of poor outcomes in individuals with many types of malignancies and other disorders (10-16). Much research revealed that a higher SII is preferable to NLR and PLR for reflecting the balance of the host's inflammatory and immune condition.

Intensive care scoring systems are used to standardize patient participation in clinical trials and compare the effectiveness of intensive care units (ICU) by predicting recovery from illness, assessing the severity of the disorders and the degree of organ dysfunction, and evaluating treatments (17,18). In scoring, patient records from regular analyses are utilized and many clinical rating systems are defined. These systems consist of two parts: "prognostic" for predicting mortality, and "organ failure" scoring systems to assess morbidity. One of the many in ICU scoring systems is Acute Physiology and Chronic Health Evaluation-II (APACHE-II), which classifies disease severity (19). APACHE-II assess acute physiology, age, and chronic health and outcomes from these three segments collected and patient mortality was calculated. Data used in APACHE-II are the values that differ most from average in the first 24 h in the ICU. The chronological age reveals the decline in physical backup and is a significant feature in determining the possibility of death in acute illness, irrespective of illness severity. For this reason, it has been added as a weighted score. In APACHE-II, when the total score is 25, estimated mortality is 25% and, when the score is above 35, this prediction value rises above 80% (20,21). This recording method has some shortcomings. Aging patients can receive a score greater than needed. There are no regulated measurements for mechanical ventilation or the medications for hemodynamic care treatment in the acute physiology score. Additional studies of predicting mortality among these elder critical patients should be undertaken (22,23). This study was designed to retrospectively explore the association among APACHE-II score and mortality in patients hospitalized in the anesthesia and reanimation ICU of a tertiary hospital.

METHODS

This study included data on patients who go through ICU in the anesthesia and reanimation department of a third hospital between January-December 2019. The hospital information system (HIS) was used to obtain information on the clinical features, lab test findings, and clinical outcomes of the patients who were enrolled. The HIS was used to obtain information on the clinical features, lab test findings, and clinical outcomes of the patients who were enrolled. Adult patients and a diagnosis-requiring ICU hospitalization were the inclusion criteria. Exclusion criteria were attendance of malignancies and coexisting chemotherapy and immunosuppressive usage, patients using drugs or blood products that affect the CBC, under 18, pregnancy, and lack of necessary data. Consequently, data of 201 patients were involved in the final study.

In accordance with the Declaration of Helsinki, data were obtained from hospital records after the patients gave their consent to share their data and the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee approved the collection (decision no: 2022-160, date: 07.09.2022). Age, gender, previous medical history, ICU risk factors, APACHE-II score, therapeutic care, and laboratory assessment were recorded. After being admitted to the ICU, all parameters were measured within 24 h. In the laboratory, Sysmex XE-5000 was used for CBC measurement. In the presence of preanalytical factors such as holding, clotting, and transfer conditions that adversely affect the platelet count, the sample was rejected and not analyzed. No technical abnormalities or flags were noted on resulting screening of Sysmex XE-5000.All patients were

then monitored for 30 days. Retrospective records of the clinical outcomes were analysed as related to SII.

The SII was calculated from the platelet (reference range: 150-400×10^3/μL), neutrophil (reference range: 1.8-6.98×10^3/μL), and lymphocyte (reference range: 1.26-3.35×10^3/μL), counts using the formulation: SII = platelet × neutrophil/lymphocyte counts as defined previously (9). The SII was expressed as ×10^3/μL. The relationship between the SII and the APACHE-II score at the time of admission to the ICU and 30-day mortality was examined. The efficacy of SII and other hemogram parameters in determining ICU mortality was investigated using the "receiver operating characteristic (ROC) curve." Sensitivity and specificity were calculated according to standard formulas (24). In comparing the results, the area under the curve (AUC) in the ROC analysis was calculated (the value must be between 0.5-1.0 for it to be significant; 1.0 indicates the most significant relationship).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). Categorical variables were expressed as numbers and percentages. Mann-Whitney U test was used to compare the numerical variables with non-normally distributed between the two groups. Non-normally distributed numerical variables are expressed as medians [minimum-maximum (max)]. In a comparison of categorical data, chi-square and Fisher's Exact chi-square tests were used. The relationship between numerical variables was evaluated with Spearman correlation analysis. In statistical analysis, $p<0.05$ (*) value was set as significant. The relationship between SII and 30-day mortality was also estimated with Cox proportional hazard regressions, and the consequences were shown as hazard ratios (HR) and 95% confidence intervals (CIs).

RESULTS

The study population consisted of 201 patients, 104 females (51.7%) and 97 males (48.3%). The median age was 73 [interquartile range (IQR): 61-82] years old. Comorbid disease was present in 95.5% (n=179) of the study population. The max shared comorbidities are hypertension (50.7%; n=102), diabetes mellitus (40.1%; n=81), chronic kidney disease (28.8%; n=58), coronary artery disease (24.3%; n=49). Pneumonia (n=67, 33.3%) was the most common cause for admission to the ICU, and sepsis developed in 35.2% (n=71) of the patients. The median length of stay in the ICU was 19 days (IQR: 8-32). It was determined that 29.32% of the patients (n=59) died from various reasons in the 30-day survival. Survivors had significantly longer hospital stays than non-survivers (median: 24 days, IQR: 14-36 days vs.15 days, IQR 12-19 days). The baseline characteristics and related information between survivors and non-survivors are presented in Table 1. Also, the distribution of APACHE-II scores and laboratory findings of the patients on admission to the ICU according to survival are shown in Table 1. SII was significantly higher in the non-survivor cohort (median; 1,566; IQR: 812-3,455 vs. 1,019; IQR 599-1,771, p=0.001). The HR (95% CI) for the high-SII group compared with the low-SII group for 30-day all-cause mortality was 2.61 (1.33, 4.79), and 1.23 (0.71, 2.61) respectively (Table 2). The sensitivity of SII over 1635 in determining mortality was 78.6%, and the specificity was 71.8%. The AUC in ROC analysis for SII was calculated as 0.823 (95% CI: 0.789-0.856).

DISCUSSION

Ratios derived from hemogram, which have been frequently used recently, can be an efficient implement in enabling the initial classification of patients in the ICU. We conducted a retrospective observational data study to investigate the capability of a SII to predict in-ICU mortality. Using Cox regression models, we observed a positive correlation between SII and all-cause mortality in ICU patients. Recently, SII, that involves three important immune cells, including neutrophil, lymphocyte, and platelet, is regarded as a good predictor of both local immunological response and systemic inflammation. This ratio can also be predictive in intensive care patients in terms of feasibility, ease of use and usability. Prognostic scoring systems are analyses of illness severity implemented to anticipate outcomes, usually mortality, of patient populations in the ICU (23). APACHE-II is one of the "prognostic scoring systems" that is widely used in ICUs and estimate mortality by evaluating the severity of the disease. The most important deficiency of APACHE-II is the lack of evaluation criteria for haemodynamic support therapy and mechanical ventilation. In addition to clinical scoring systems, the predictive contribution of indices obtained from the CBC can enable appropriate analyses and treatment to be occupied initially during the clinical progression.

Leukocytes create a physiological response to stress, and this response is manifested by a proliferation of neutrophils and a decline of lymphocytes. Although the main task of platelets is on the hemostasis and coagulation system, an increase in the proliferation of the megakaryocytic lineage and a consequent increase in the number of platelets are observed in chronic inflammatory processes. The lymphocyte count tends to decrease due to increased apoptosis. All these values are a single collection under

Table 1. Comparisons of baseline characteristics and lab findings between the survive and the non-survive group

Parameter	All cohort (n=201)	Survivors (n=142)	Non-survivors (n=59)	p-value
Demographics				
Age, years (median, IQR)	73 (61-82)	69 (61-78)	79 (74-82)	0.**001**
Gender, n (%)				
Male	97 (48.3%)	66 (68.1%)	31 (31.9%)	0.211
Female	104 (51.7%)	76 (73%)	28 (27%)	-
Comorbidities, n (%)				
Hypertension	102 (50.7%)	69 (48.6%)	33 (55.9%)	0.117
Diabetes mellitus	81 (40.1%)	54 (38%)	27 (45.7%)	0.322
Chronic kidney disease	58 (28.8%)	38 (26.7%)	20 (33.8%)	0.172
Coronary artery disease	49 (24.3%)	33 (23.2%)	16 (27.1%)	0.205
ICU admission reasons n (%)				
Pneumonia	67 (33.3%)	39 (27.4%)	28 (47.45%)	**0.012**
Acute kidney disease	25 (12.1%)	17 (11.9%)	8 (13.55%)	0.125
Gastrointestinal event	31 (25.4%)	24 (16.9%)	7 (11.8%)	0.119
Others	78 (38.8%)	-	-	-
Sepsis	71 (35.2%)	-	-	-
Length of ICU stay, days (IQR)	19 (8-32)	24 (14-36)	15 (12-19)	**0.021**
APACHE-II	19 (5-43)	18 (6-41)	20 (7-43)	0.204
Lab findings on admission				
Hemoglobin, g/dL	10.90 (9.80-12.20)	11.20 (9.60-12.40)	10.60 (9.30-11.70)	**0.023**
WBC ($\times 10^3$ µL)	10.75 (5.00-15.32)	11.05 (5.20-14.30)	9.640 (4,80-19.60)	**0.014**
Neutrophils ($\times 10^3$ µL)	8.14 (9.20-10.48)	8.10 (6.66-9.40)	8.90 (6.60-12.20)	0.12
Lymphocytes ($\times 10^3$ µL)	1.10 (0.65-1.25)	1.15 (0.80-1.20)	0.80 (0.70-1.00)	**0.033**
Monocytes ($\times 10^3$ µL)	0.45 (0.30-0.60)	0.50 (0.35-0.65)	0.35 (0.25-0.55)	0.62
Platelets ($\times 10^3$ µL)	214 (172-275)	225 (179-267)	194 (165-255)	0.45
SII (median, IQR)	**1,148 (756-2,483)**	**1,019 (599-1,771)**	**1,566 (812-3,455)**	**0.037**

All continuous variables are reported as medians and IQRs. Statistical significance set at 0.05.
ICU: Intensive care unit, WBC: White blood cells, SII: Systemic immune inflammation index, IQR: Interquartile range, APACHE-II: Acute Physiology and Chronic Health Evaluation-II

the parameter-formed SII. It has been suggested in recent publications that this value, which is formed from whole blood parameters involved in the inflammation process, should be used as an indicator of inflammation. In a study by Dey et al. (25), assumed the collective impact of pro-inflammatory and pro-thrombotic corpuscular lines in calculating the new indices, SII represents a modest and reproducible factor representing the possible of describing the patients susceptible to poor results later off-pump coronary artery bypass grafting (26). It has been reported that SII, which is one the inflammatory parameters, cheap and easily available, can be a good predictor in predicting

Table 2. Cox regression analysis for the risk factors associated with 30-day mortality

Variables	30-day mortality		p-value
	HR	95% CI	
Age (per 1 year increase)	1.03	1.01-1.12	**0.014**
APACHE-II			
<18	1	-	-
>20	1.49	0.31-4.73	0.151
SII			
<1,019	1	-	-
1,019-1,566	1.21	0.73-2.67	**0.013**
>1,566	2.61	1.33-4.79	**0.011**

All statistically significant values are reported in bold.

HR: Hazard ratio, CI: Confidence interval, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SII: Systemic immune-inflammation index

most important adverse cardiac and cerebral accidents later bypass surgery (26). In the other study intended to elucidate the possible prognostic meaning of SII, expressed it effectively predicts 30- and 90-day mortality and the great risk of the existence of main cardiac adverse actions (27). It was stated that in coronavirus disease-2019 patients, SII at admission independently predicted in-hospital mortality and helped with early risk stratification in this group (28,29). SII is also a possibly valuable predictive tool for acute pancreatitis that is an illness defined as acute inflammation of the pancreas (30). The index of SII may guess intravenous immunoglobulin resistance, myocarditis, valve regurgitation in Kawasaki disease as a specific factor (31). SII has also been recognized as a predictive marker in several cancers (10-13). In most of these studies, SII was preferable to other indices. The cause for the advantage of the SII can be explained in the following way: there is a lymphopenia, and this is due to augmented inflammatory response and high cortisol levels triggered by an enlarged sympathetic activity. The increased neutrophil count is thought to be subordinate to the increased inflammatory response. The inflammatory reaction may be tributary to increased oxygen radicals due to hypoxia-induced reperfusion injury or may be related with a thorough increase in interleukin (IL)-6, IL-8, P-selectin, tumor necrosis factor alpha in inflammatory cells because of endothelial damage (32). Enlarged platelet in patients might be related to platelet activation. This is due to inflammation or associated with increased catecholamine secretion induced by comorbidity, high oxidative stress and endothelial damage. Therefore, SII is accepted as a parameter that shows both high neutrophil levels reflecting acute inflammation, low lymphocyte levels reflecting physiological stress, and negative effects of thrombocytosis induced by endothelial damage.

CONCLUSION

In our study, the multivariate Cox regression models showed that the SII was significantly related to survival after correction for age, and APACHE score. This index has only three components, is easily calculated and inexpensive. The fact that our study was retrospective conducted at a single center and therefore only included few patients is its most significant limitation. Another limitation is due to the study's retrospective design, the effects of highly sensitive inflammatory parameters like IL-6, procalcitonin, and C-reactive protein could not be assessed. To understand the mechanism of SII's impact on poor results, prospective studies involving many patients are required.

ETHICS

Ethics Committee Approval: In accordance with the Declaration of Helsinki, data were obtained from hospital records after the patients gave their consent to share their data and the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee approved the collection (decision no: 2022-160, date: 07.09.2022).

Informed Consent: Retrospective study.

Authorship Contributions

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

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

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

REFERENCES

1. Jacob EA. Complete blood cell count and peripheral blood film, its significant in laboratory medicine: a review study. American Journal of Laboratory Medicine 2016;1:34-57.
2. Qin G, He F, Zhang H, Pazo EE, Dai G, Yao Q, et al. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) are more prominent in retinal artery occlusion (RAO) compared to retinal vein occlusion (RVO). PLoS One 2022;17:e0263587.
3. Balta S, Demirkol S, Unlu M, Arslan Z, Celik T. Neutrophil to lymphocyte ratio may be predict of mortality in all conditions. Br J Cancer 2013;109:3125-6.
4. Pantzaris ND, Platanaki C, Pierrako C, Karamouzos V, Velissaris D. Neutrophil-to-lymphocyte Ratio Relation to Sepsis Severity Scores and Inflammatory Biomarkers in Patients with Community-acquired Pneumonia: A Case Series. J Transl Int Med 2018;6:43-6.
5. Ceyhun HA, Gürbüzer N. New Hematological Parameters as Inflammatory Biomarkers: Systemic Immune Inflammation Index,

Platerethritis, and Platelet Distribution Width in Patients with Adult Attention Deficit Hyperactivity Disorder. Adv Neurodev Disord 2022;6:211-23.

6. Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, Clarke SJ. A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. Br J Cancer 2012;107:695-9.
7. Kang MH, Go SI, Song HN, Lee A, Kim SH, Kang JH, et al. The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer. Br J Cancer 2014;111:452-60.
8. Cho KM, Park H, Oh DY, Kim TY, Lee KH, Han SW, et al. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and their dynamic changes during chemotherapy is useful to predict a more accurate prognosis of advanced biliary tract cancer. Oncotarget 2017;8:2329-41.
9. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014;20:6212-22.
10. Coutu BG, Johnson KC, Bhirud A, Baine MJ, Zhen W, Zhang C, et al. Systemic Immune-Inflammatory Index Association with Survival in Patients Undergoing Trimodality Therapy for Lung Cancer. Oncology 2022;100:247-56.
11. Fu H, Zheng J, Cai J, Zeng K, Yao J, Chen L, et al. Systemic Immune-Inflammation Index (SII) is Useful to Predict Survival Outcomes in Patients After Liver Transplantation for Hepatocellular Carcinoma within Hangzhou Criteria. Cell Physiol Biochem 2018;47:293-301.
12. Wang Q, Zhu D. The prognostic value of systemic immune-inflammation index (SII) in patients after radical operation for carcinoma of stomach in gastric cancer. J Gastrointest Oncol 2019;10:965-78.
13. Mirili C, Paydas S, Kapukaya TK, Yılmaz A. Systemic immune-inflammation index predicting survival outcome in patients with classical Hodgkin lymphoma. Biomark Med 2019;13:1565-75.
14. Ustundag Y, Huysal K, Gecgel SK, Unal D. Relationship between C-reactive protein, systemic immune-inflammation index, and routine hemogram-related inflammatory markers in low-grade inflammation. Int J Med Biochem 2018;1:24-8.
15. Wu S, Shi X, Zhou Q, Duan X, Zhang X, Guo H. The Association between Systemic Immune-Inflammation Index and All-Cause Mortality in Acute Ischemic Stroke Patients: Analysis from the MIMIC-IV Database. Emerg Med Int 2022;2022:4156489.
16. Ren B, Chen X, Lei P, Hou L, Wang H, Zhou Y, et al. The Relationship Between Preoperative Systemic Immune Inflammation Index and Prognostic Nutritional Index and the Prognosis of Patients With Alveolar Hydatid Disease. Front Immunol 2021;12:691364.
17. Bouch DC, Thompson JP. Severity scoring systems in the critically ill. Continuing education in anaesthesia, critical care & pain 2008;8:181-5.
18. Keegan MT, Gajic O, Afessa B. Severity of illness scoring systems in the intensive care unit. Crit Care Med 2011;39:163-9.
19. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
20. Zou X, Li S, Fang M, Hu M, Bian Y, Ling J, et al. Acute Physiology and Chronic Health Evaluation II Score as a Predictor of Hospital Mortality in Patients of Coronavirus Disease 2019. Crit Care Med 2020;48:e657-65.
21. Singh P, Pathak S, Sharma RM. A Comparison of Acute Physiology and Chronic Health Evaluation III and Simplified Acute Physiology Score II in Predicting Sepsis Outcome in Intensive Care Unit. Anesth Essays Res 2018;12:592-7.
22. Wang ZC, Jiang W, Chen X, Yang L, Wang H, Liu YH. Systemic immune-inflammation index independently predicts poor survival of older adults with hip fracture: a prospective cohort study. BMC Geriatr 2021;21:155.
23. Kelley MA. Manaker S, Finlay G, editors. Predictive scoring systems in the intensive care unit. UpToDate. Available from: https://www.uptodate.com/contents/predictive-scoring-systems-in-the-intensive-care-unit
24. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem 1993;39:561-77.
25. Dey S, Kashav R, Kohli JK, Magoon R, ItiShri, Walian A, et al. Systemic Immune-Inflammation Index Predicts Poor Outcome After Elective Off-Pump CABG: A Retrospective, Single-Center Study. J Cardiothorac Vasc Anesth 2021;35:2397-404.
26. Abanoz M, Engin M. Investigation of systemic immune inflammatory index and prognostic nutritional index in prediction of major adverse cardiovascular and cerebral events occurring after coronary artery bypass operations. Acta Medica Alanya 2021;5:263-9.
27. Tang Y, Zeng X, Feng Y, Chen Q, Liu Z, Luo H, et al. Association of Systemic Immune-Inflammation Index With Short-Term Mortality of Congestive Heart Failure: A Retrospective Cohort Study. Front Cardiovasc Med 2021;8:753133.
28. Fois AG, Paliogiannis P, Scano V, Cau S, Babudieri S, Perra R, et al. The Systemic Inflammation Index on Admission Predicts In-Hospital Mortality in COVID-19 Patients. Molecules 2020;25:5725.
29. Asaduzzaman MD, Bhuia MR, Alam ZN, Bari MZJ, Ferdousi T. Role of hemogram-derived ratios in predicting intensive care unit admission in COVID-19 patients: a multicenter study. IJID Reg 2022;3:234-41.
30. Zhang D, Wang T, Dong X, Sun L, Wu Q, Liu J, et al. Systemic Immune-Inflammation Index for Predicting the Prognosis of Critically Ill Patients with Acute Pancreatitis. Int J Gen Med 2021;14:4491-8.
31. Liu X, Shao S, Wang L, Zhang N, Wu M, Liu L, et al. Predictive Value of the Systemic Immune-Inflammation Index for Intravenous Immunoglobulin Resistance and Cardiovascular Complications in Kawasaki Disease. Front Cardiovasc Med 2021;8:711007.
32. Zheng J, Cai J, Li H, Zeng K, He L, Fu H, et al. Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Prognostic Predictors for Hepatocellular Carcinoma Patients with Various Treatments: a Meta-Analysis and Systematic Review. Cell Physiol Biochem 2017;44:967-81.