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okarabay@sakarya.edu.tr
GSM: +90 5422431670
Sakarya Üniversitesi Tıp Fakültesi Enfeksiyon Hastalıkları Anabilim Dalı, Sakarya, Türkiye

Prof. Dr. Süleyman KALELİ
skaleli@sakarya.edu.tr
GSM: +90 536 549 11 61
Sakarya Üniversitesi Tıp Fakültesi, Sakarya, Türkiye

Doç. Dr. Nevin İNCE
drnevince@gmail.com
GSM: +90 505 350 58 39
Düzce Üniversitesi Tıp Fakültesi, Düzce, Türkiye

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):189-194 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):189-194*

Evaluation of Rockall and Blatchford Scores and Forrest Staging in Upper Gastrointestinal Bleeding

Üst Gastrointestinal Sistem Kanamalarında Rockall ve Blatchford Skorları ile Forrest Evrelemenin Değerlendirilmesi

[1]Seda KUMBASAR, [1]Semra ÖZKAN ÖZTÜRK

[1]Mersin City Training and Research Hospital, Department of Internal Medicine, Mersin, Türkiye

Semra Özkan Öztürk: https://orcid.org/0000-0003-2223-197X
Seda Kumbasar: https://orcid.org/0000-0002-0280-0533

ABSTRACT

Objective: The study aimed to investigate the predictive value of Rockall and Blatchford scores and endoscopic Forrest staging in the need for transfusion and intensive care in upper gastrointestinal bleeding.

Materials and Methods: This retrospective study was conducted on 294 patients with gastrointestinal bleeding who presented to the emergency department between January 1 and June 1, 2013.

Results: The mean age of 294 patients was 58.73±21.30 years. The endoscopic diagnoses of the patients included peptic ulcer (43.5%, n=128), erosive gastritis (17.3%, n=51), and erosive bulbitis (12.6%, n=37). There was no statistically significant relationship between Forrest staging and Rockall and Blatchford scores (p=0.944, p=0.757). The need for blood transfusion was significantly more frequent in patients with a Rockall score of 5 and above and those with a high Blatchford score (p=0.004, p=0.001). Patients with a Rockall score of 5 and above were significantly more common among those referred to the intensive care unit (p=0.003).

Conclusion: Pre-endoscopic Rockall and Blatchford scores and endoscopic Forrest staging can be used safely in predicting transfusion requirement, intensive care requirement, mortality risk, treatment and follow-up of patients with gastrointestinal bleeding, and thus may help to reduce health expenditures.

Keywords: Blatchford score, Forrest staging, Rockall score, upper gastrointestinal bleeding

ÖZ

Amaç: Bu çalışmada Rockall ve Blatchford skorlarının ve endoskopik Forrest evrelemesinin üst gastrointestinal sistem kanamalarında transfüzyon gereksinimi, yoğun bakım gereksinimi ön görmede etkisinin incelenmesi amaçlanmıştır.

Materyal ve Metot: Bu retrospektif çalışma 1 Ocak-1 Haziran 2013 tarihleri arasında acil servise başvuran 294 gastrointestinal kanamalı hasta üzerinde yapılmıştır.

Bulgular: 294 hastanın yaş ortalaması 58,73±21,30'dur. Hastaların endoskopik tanılarına bakıldığında olguların % 43,5'inde (n=128) peptik ülser, %17,3'ünde (n=51) eroziv gastrit ve %12,6'sında (n=37) eroziv bulbit olduğu görülmüştür. Forrest evrelemesi ile Rockall ve Blatchford skorları arasında istatistiksel olarak anlamlı bir ilişki bulunmamaktadır (p=0,944, p=0,757). Rockall skoru 5 ve üzerinde olanların, Blatchford skoru yüksek olanların kan transfüzyon ihtiyacı anlamlı şekilde yüksektir. (p=0,004, p=0,001). Yoğun bakıma sevk olan olguların Rockall skorlarının 5 ve üzerinde olma oranı (%61,5), taburcu olan olgulardan (%22,9) anlamlı şekilde yüksektir (p=0,003).

Sonuç: Endoskopi öncesi Rockall ve Blatchford skorları ile endoskopik Forrest evrelemesi gastrointestinal kanamalı hastaların transfüzyon gereksinimi, yoğun bakım gereksinimi, mortalite riskini ön görmede, hastaların tedavi ve takibinde güvenle kullanılabilir, dolayısıyla sağlık harcamalarının azaltılmasına yardımcı olabilir.

Anahtar Kelimeler: Blatchford skoru, Forrest evrelemesi, Rockall skoru, üst gastrointestinal sistem kanaması

Sorumlu Yazar / Corresponding Author:
Seda Kumbasar,
Mersin City Training and Research Hospital Korukent District Toroslar / Mersin, Türkiye.
Tel: +905057506995
E-mail: sedadabakoglu@hotmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 04/07/2024
Kabul Tarihi/ Accepted: 14/08/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Kumbasar S and Özkan Öztürk S. Evaluation of Rockall and Blatchford Scores and Forrest Staging in Upper Gastrointestinal Bleeding. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):189-195. doi: 10.26453/otjhs.1322785

INTRODUCTION

Upper gastrointestinal bleeding is an important cause of mortality and morbidity. Upper gastrointestinal bleeding occurs in the proximal part of the ligament of Treitz.[1,2] Although up to 80% of the cases recover spontaneously, the mortality rate can reach as high as 10%. It requires very rapid assessment and medical intervention from the moment of presentation to the emergency department. According to a study, the leading causes of cost in gastrointestinal bleeding were hospitalization, endoscopic procedures, and blood transfusion. Over time, many risk scoring systems have been developed to predict the risk of rebleeding and mortality based on clinical parameters, comorbidities, and laboratory and endoscopy findings to reduce patient costs.[3-5] Forrest classification is one of the most widely used classifications based on endoscopic ulcer appearance.[6] The Rockall's score (RS), which includes pre-endoscopic and endoscopic components, is useful in predicting mortality.[7] Another common scoring system is the Glasgow-Blatchford scoring (GBS) system, which uses only clinical and laboratory findings to predict low-risk patients who do not require intervention.[8]

This study aimed to investigate the predictive value of pre-endoscopic Rockall and Blatchford scores and endoscopic Forrest classification on transfusion requirement, intensive care requirement, and follow-up and treatment planning in upper gastrointestinal bleeding.

MATERIALS AND METHODS

Ethics Committee Approval: The study was approved by the Ümraniye Training and Research Hospital Ethics Committee (Date: 05/07/2013, decision no: 2013-9563). The study was planned under the Helsinki Principles.

Study Design:

Subjects: The study enrolled 296 patients with upper gastrointestinal bleeding admitted to the gastroenterology clinic at Ümraniye Training and Research Hospital between January 1 and June 1, 2013.

Data Collecting: Detailed information was collected for each patient, including demographic data, vital signs, comorbidities, medication usage, physical examination findings, laboratory parameters, need for blood transfusion, intensive care requirement, surgical or endoscopic interventions, and in-hospital mortality.

Evaluation of Data: The Blatchford's score was determined for every patient using eight clinical or laboratory variables, including systolic blood pressure, heart rate, blood urea nitrogen level, hemoglobin level, presentation with melena, presentation with syncope, presence of liver disease, and heart failure. In the Blatchford scoring system, the maximum score that a patient can receive is 23 points and is accordingly defined as low/high risk (6 and above high).[8] The pre-endoscopic Rockall's score was determined for patients without endoscopic findings, considering age at presentation, heart rate, systolic blood pressure, and comorbid diseases. The Rockall's score was then determined by incorporating the endoscopic findings (endoscopic diagnosis and signs of recent bleeding) into these parameters. Pre-endoscopic Rockall score is calculated according to age, tachycardia, hypotension, and presence of comorbidities (renal failure, liver failure, malignancy). In Rockall scoring, 0-2 is defined as low risk, 3-4 as moderate risk and above 5 as high risk.[7] Endoscopically, Forrest classification includes active oozing (Forrest IA), active leaking (Forrest IB) and non-bleeding visible vessel (Forrest IIA), peptic ulcers with adhesive clots (Forrest IIB lesion), red-stained (Forrest IIC), or clear-bottomed (Forrest IIB) ulcers. Forrest III) in the form of ulcers.[6] All patients underwent endoscopy, and the Forrest classification was applied.

Statistical Analysis: The IBM SPSS Statistics 22.0 program was used for statistical analysis. In addition to descriptive statistical methods (mean, standard deviation, frequency), the Kruskal-Wallis test was used to compare quantitative variables between groups. The Mann-Whitney U test was used to determine the group that caused the difference. The Mann-Whitney U test was used to compare variables between the two groups. Chi-square and Continuity Correction (Yates) tests were used to compare qualitative data. Spearman's rho correlation analysis was used to examine the relationships between the parameters. $P<0.05$ was accepted as statistically significant in all analyses.

RESULTS

Patients were between 18-94 years of age, with a mean age of 58.73±21.30 years. Of the patients, 70% (n=206) were male and 30% (n=88) were female. The duration of hospitalization ranged between 1 day and 20 days, with a mean of 5.10±3.28 days. While 95.2% (n=280) of the patients were discharged, 4.4% (n=13) were referred to the intensive care unit, and one patient died. The endoscopic diagnoses of the patients included peptic ulcer (43.5%, n=128), erosive gastritis (17.3%, n=51), and erosive bulbitis (12.6%, n=37). The general characteristics and endoscopic diagnosis distribution of the patients are shown in Table 1.

When the Forrest classification of the patients was examined, it was seen that 85.7% of them were grade 3, 7.4% were grade 2B, 5.4% were grade 2C, 3.7% were grade 1A, and 2.7% were grade 2A. Rockall scores of the patients ranged between 0 and

Table 1. General characteristics of patients and distribution of endoscopic diagnosis.

Characteristics		**Data**
Age, Mean ± SD (Min-Max)		58.73±21.30(18-94)
Length of stay in hospital (day), Mean ± SD (Min-Max)		5.10±3.28 (1-20)
Transfer to intensive care		13 (4.4)
Gender, n (%)	Male	88(30)
	Female	206 (70)
Endoscopic diagnosis, n (%)	Peptic ulcer	128 (43.5)
	Erosive gastritis	51 (17.3)
	Malignant	18 (6.1)
	Esophageal varices	11 (3.7)
	Esophagitis	25 (8.6)
	Mallory-Weiss	8 (2.8)
	Polypoid lesion	6 (2)
	Angiodysplasia	10 (3.4)
	Erosive bulbitis	37 (12.6)

SD: Standard Deviation; Min: Minimum; Max: Maximum.

7 with a mean of 3.05±1.67. Rockall score was 0-2 in 42.2% (n=124), 3-4 in 33.3% (n=98), and 5 and above in 24.5% (n=72) of the patients. The Blatchford's score of the patients ranged between 3 and 17 with a mean of 11.37±2.72. 55.1% (n=162) of the patients had a low Blatchford's score, whereas 44.9% (n=132) had a high score. The distribution of Forrest classification, Rockall and Blatchford scores of the patients is shown in Table 2.

There was no statistically significant relationship between the Forrest classification and Rockall's score (p=0.900). There was no statistically significant relationship between the Forrest classification and Blatchford's score (p=0.510). Correlation analysis results are shown in Table 3.

Table 2. Distribution of Patients' Forrest classification, Rockall and Blatchford scores.

Scores and Classification		**n (%)**
Forrest Classification (grade)	1 A	11 (3.7)
	2 A	8 (2.7)
	2 B	7 (7.4)
	2 C	16 (5.4)
	3	252 (85.7)
Rockall Score	0-2	124 (42.2)
	3-4	98 (33.3)
	≥ 5	72 (24.5)
Blatchford Score	Low	162 (55.1)
	High	132 (44.9)

Table 3. Relationship between Forrest classification and Rockall and Blatchford scores.

Scores		**Forrest Classification**					**p***
		1A	**2A**	**2B**	**2C**	**3**	
		n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Rockall's Score	**0-2**	3 (27.3)	5 (62.5)	3 (42.9)	7 (43.8)	106 (42.1)	0.900
	3-4	4 (36.4)	1 (12.5)	2 (28.6)	6 (37.5)	85 (33.7)	
	≥ 5	4 (36.4)	2 (25)	2 (28.6)	3 (18.8)	61 (24.2)	
Blatchford's Score	**Low**	4 (36.4)	6 (75)	3 (42.9)	9 (56.3)	140 (55.6)	0.510
	High	7 (63.6)	2 (25)	4 (57.1)	7 (43.8)	112 (44.4)	

*: Chi-Square test.

A statistically significant difference was found in duration of hospitalization according to Rockall's score (p=0.009). Length of hospitalization was significantly longer for patients with a Rockall's score of 5 and above compared to patients with a Rockall's score of 0-2 (p:0.003; p<0.01) and 3-4 (p:0.030; p<0.05). Regarding length of hospitalization, no significant difference was found between patients with a Rockall's score of 0-2 and patients with a Rockall's score of 3-4 (p:0.306; p>0.05). No significant relationship was found between the length of hospitalization and Blatchford's score (p=0.062). Similarly, no significant relationship was found between the length of hospitalization and the Forrest classification (p=0.156). However, there was a statistically significant relationship between the need for blood transfusion and Rockall's score (p<0.05). A significantly higher ratio of patients needing blood transfusion had a Rockall's score of 5 and above (28.5%) compared to patients who did not need blood transfusion (18.3%). There was a statistically significant relationship between the need for blood transfusion and Blatchford's score (p<0.01). A significantly higher ratio of patients needing blood transfusion had a higher Blatchford's score (56.4%) than patients who did not need blood transfusion (27%). Analysis results for the relationship between the need for blood transfusion and length of hospitalization with Rockall and Blatchford scores are shown in Table 4.

A statistically significant relationship existed between referral to the intensive care unit or discharge status and Rockall's score (p=0.003). A significantly higher ratio of patients referred to the intensive care unit had a Rockall's score of 5 and above (61.5%) compared to those discharged (22.9%). No statistically significant relationship existed between referral to the intensive care unit or discharge and Blatchford's score (p=0.055). Analysis results for the relationship between intensive care unit referral and discharge status and patient scores are shown in Table 5.

Table 4. Relationship between blood requirement, duration of hospitalization and Forrest classification, Rockall and Blatchford scores.

Scores and Classification		**Blood transfusion requirement**		**Duration of hospitalization (day) Mean±SD (median)**
		No n (%)	**Yes** n (%)	
Rockall's Score	**0-2**	60 (52.2)	64 (35.8)	4.52±2.86 (4)
	3-4	34 (29.6)	64 (35.8)	4.85±2.77 (4)
	≥ 5	21 (18.3)	51 (28.5)	6.44±4.18 (5)
P value		**[1] 0.016***		**[2]0.009***
Blatchford's Score	**Low**	84 (73.0)	78 (43.6)	4.82±3.21 (4)
	High	31 (27.0)	101 (56.4)	5.44±3.37 (5)
P value		**[1]0 .001***		**[3]0.062**
Forrest Classification (grade)	**1 A**	0 (0)	11(6.1)	5.45±3.78 (5)
	2 A	0(0)	8 (4.4)	3.38±1.50 (3.5)
	2 B	0 (0)	7 (3.9)	7.57±4.89 (7)
	2 C	0 (0)	16 (8.8)	5.19±2.66 (5)
	3	115(100)	137 (76.8)	5.06±3.27 (4)
P value		**[1] 0.001***		**[2]0.156**

[1]: Ki-kare test; *: p<0.05; [2]: Kruskal Wallis Test; [3]: Mann Whitney U test.

Table 5. Relationship between transfer to intensive care unit and Forrest classification, Rockall and Blatchford scores.

Scores and Classification		**Transfer to intensive care unit n (%)**	**p-value**
Rockall's Score	**0-2**	1 (7.7)	**[1]0.003****
	3-4	4 (30.8)	
	≥ 5	8 (61.5)	
Blatchford's Score	**Low**	6 (46.2)	[2]0.714
	High	7 (53.8)	
Forrest Classification (grade)	**1 A**	11(84.6)	**[1]0.001****
	2 A	2(15.4)	
	2 B	0(0)	
	2 C	0(0)	
	3	0(0)	

[1]: Kruskal Wallis Test; [2]: Mann Whitney U test; **: p<0.01.

DISCUSSION AND CONCLUSION

Upper gastrointestinal bleeding is life-threatening and requires rapid intervention. Various risk scores have been developed that can help in rapid decision-making to determine bleeding severity, determine the urgency of endoscopy, identify the need for blood transfusion, and control bleeding. Studies have reported that the incidence of upper gastrointestinal bleeding in men is approximately twice that of women.[9-11] Similarly, males constituted 70% of the patients in our study.

In our study, no statistically significant difference was found in the length of hospitalization concerning Blatchford's score and Forrest's classification. A statistically significant difference was found in duration of hospitalization according to Rockall's score ($p=0.009$). Length of hospitalization was significantly longer for patients with a Rockall's score of 5 and above compared to patients with a Rockall's score of 0-2 ($p:0.003$; $p<0.01$) and 3-4 ($p:0.030$; $p<0.05$). In terms of length of hospitalization, no significant difference was found between patients with a Rockall's score of 0-2 and patients with a Rockall's score of 3-4 ($p:0.306$; $p>0.05$). In several studies, high Rockall and Blatchford scores were found to be associated with length of hospitalization.[11-13] In contrast, two studies concluded that Rockall and Blatchford scores were not associated with length of hospital stay.[14,15] In another study, a high Rockall's score was found to be associated with the length of hospitalisation.[16] These results are consistent with our study.[16] The high Rockall's score was more successful than Blatchford's score and Forrest's classification in predicting the length of hospitalization.

In different studies, a high Rockall's score was found to be associated with the need for blood transfusion.[17,18] In three other studies, high Rockall and Blatchford scores were found to be associated with the need for blood transfusion.[10,11,15,19] In another study comparing risk scores and shock indices, Glasgow-Blatchford's score was found to be the most successful predictor of major transfusion and endoscopic treatment needs.[20-22] In our study, a significantly higher ratio of patients requiring blood transfusion had a Rockall's score of 5 and above. Similarly, Blatchford's score was significantly higher in patients requiring blood transfusion. Our results are consistent with the literature.[10,11,17-19]

In a previous study, a significant relationship was shown between high Rockall and Blatchford scores and referral to the intensive care unit.[23] In our study, the referral rate to the intensive care unit was significantly higher in patients with a Rockall's score of 5 and above. There was no significant correlation between Blatchford's score and referral to the intensive care unit.

Similarly, no significant correlation was found between the Forrest classification and Rockall and Blatchford scores. There is no study in literature, which evaluates the relationship between these three scoring systems.

In conclusion, the combined use of the Rockall and Blatchford scores, and Forrest classification in follow-up and treatment planning may increase the success of treatment in patients with upper gastrointestinal bleeding. Therefore, it can help reduce healthcare expenses. The limitations of this study include its retrospective design and the fact that it was conducted in a single center. Prospective studies are needed to confirm the applicability of these scores in upper gastrointestinal bleeding.

Ethics Committee Approval: This study was planned following the Helsinki Principles, and ethical approval was obtained from Ümraniye Training and Research Hospital Ethics Committee (Date: 05/07/2013, Decision no: 2013-9563).

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

Author Contributions: Concept – SK, SÖÖ; Supervision – SK, SÖÖ; Materials – SK; Data Collection and/or Processing – SK; Analysis and/or Interpretation – SK, SÖÖ; Writing –SÖÖ.

Peer-review: Externally peer-reviewed.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):195-201 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):195-201*

Use of Supplementary Medicines/Nutrients and Disease Behaviours during the COVID-19 Pandemic

COVID-19 Pandemisinde Takviye İlaç/Besin Kullanımı ve Hastalık Davranışları

[1]Uçar KÜÇÜK, [2]Birsel Canan DEMİRBAĞ

[1]Trabzon University, Tonya Vocational School, Department of Medical Services and Techniques, First and Emergency Aid Program, Trabzon, Türkiye
[2]Karadeniz Technical University, Faculty of Health Sciences, Department of Nursing, Public Health Nursing, Trabzon, Türkiye

Uçar Küçük: https://orcid.org/0000-0003-0798-3401
Birsel Canan Demirbağ: https://orcid.org/ 0000-0003-4145-5020

ABSTRACT

Objective: The study was conducted to reveal which type of supplementary people used against COVID-19 disease and determine their behaviours/ideas related to the disease.

Materials and Methods: This study is a cross-sectional was conducted between April and May 2021. It was limited to people over the age of 18, and the snowball sampling method was used along with a questionnaire form.

Results: Of the individuals participating in the study, 74.4% were in the 18-33 age group, 72.6% were female, 64.6% were single, 65.8% had bachelor's degrees and associate degrees, 49.5% were actively working, and 63.13% had 1-10 years of work experience. Of the participants, 72.1% did not catch COVID-19. Medicines or supplementary nutrients are used mainly by individuals in the 34-49 age group (51.7%).

Conclusion: The most used supplementary medicines and nutrients were antiviral and anti-flu medicines and paracetamol, vitamins C, D, B, iron, omega-3, green tea, honey, thyme, ginger, lemon, spicy teas, turmeric, and fruit tea. The use of non-medicine complementary methods has increased while studies on the treatment of COVID-19 are ongoing. Among these methods, there is a tendency to mostly use supplementary medicines, nutrients, vitamins, and herbal products, respectively.

Keywords: Behaviour, COVID-19, herbal products, medicine, nutrient

ÖZ

Amaç: Araştırma, kişilerin COVİD-19 hastalığına karşı ne tür tamamlayıcı tedavi kullandığını ortaya çıkarmak ve hastalıkla ilgili davranışlarını/fikirlerini belirlemek amacıyla yapılmıştır.

Materyal ve Metot: Bu çalışma kesitsel bir çalışma olup, Nisan-Mayıs 2021 tarihleri arasında yürütülmüştür. 18 yaş üstü kişilerle sınırlı olup, anket formu ile birlikte kartopu örnekleme yöntemi kullanılmıştır.

Bulgular: Araştırmaya katılan bireylerin %74,4'ü 18-33 yaş grubunda, %72,6'sı kadın, %64,6'sı bekar, %65,8'i lisans ve önlisans mezunu, %49,5'i aktif olarak çalışıyor ve %63,13'ü 1- 10 yıllık iş tecrübesi bulunmaktadır. Katılımcıların %72,1'i COVID-19'a yakalanmamıştır. İlaç veya besin takviyesini en çok 34-49 yaş grubundaki bireyler (%51,7) kullanıyor.

Sonuç: En çok kullanılan takviye edici ilaç ve besinler ise antiviral ve grip ilaçları ile parasetamol, C, D, B vitaminleri, demir, omega-3, yeşil çay, bal, kekik, zencefil, limon, baharatlı çaylar, zerdeçal ve meyve çayları oldu. COVİD-19 tedavisine yönelik çalışmalar devam ederken ilaç dışı tamamlayıcı yöntemlerin kullanımı da arttı. Bu yöntemler arasında en çok sırasıyla tamamlayıcı ilaçlar, besinler, vitaminler ve bitkisel ürünlere yönelme eğilimi vardır.

Anahtar Kelimeler: Besin, bitkisel ürünler, COVID 19, davranış, ilaç

Sorumlu Yazar / Corresponding Author:
Uçar Küçük
Trabzon University, Tonya Vocational School, Tonya/Trabzon, Türkiye
Tel: +90538 567 78 14
E-mail: ucarkucuk@trabzon.edu.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 13/09/2023
Kabul Tarihi/ Accepted: 14/07/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Küçük U and Demirbağ BC. Use of Supplementary Medicines/Nutrients and Disease Behaviours during the COVID-19 Pandemic. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):195-201. doi: 10.26453/otjhs.1359785

INTRODUCTION

COVID-19 is a viral infection that has spread as a pandemic. The disease is transmitted through droplets. Respiratory symptoms, fever, cough, and dyspnea are the common signs of the infection.[1,2] Some patients may experience pain, nasal obstruction, nasal discharge, sore throat, or diarrhea. In some cases of infection, symptoms are not observed, and most cases (about 80%) recover without the need for medical treatment. Loss of appetite, insufficient food intake, dehydration caused by fever and hypovolemic shock accompany the main symptoms of COVID-19.[3]

While studies on medical treatment are conducted to find the most effective treatment methods, people take non-medicine supplementary measures in addition to effective vaccination and treatment methods.[4-7] The number of COVID-19 cases was 2,208,652, and the number of deaths was 20,881 in Türkiye in 2020. The number of cases was 7,156,747, and the number of deaths was 61,036 in 2021. Since COVID -19 cases started to be observed in our country, the total number of cases has been 13 million, and the number of deaths has been 94 thousand.[8]

Communities worldwide which have gone through the pandemic, and especially death, have panicked and resorted to non-medicine treatments.[9-11] Due to the difficulty in reaching and talking to healthcare professionals during the COVID-19 pandemic, information about supplementary has been obtained from the media and the internet[1]. As in many countries, social sensitivity toward supplementary has increased in our country to avoid unnecessary medicine use.[12-14] Studies on protection from COVID-19 and disease management continue rapidly all over the world. In this process, individuals can use supplementary methods to maintain their health. There are different types of supplementary methods such as chiropractic, ozone therapy, ayurveda, acupuncture, aromatherapy, homeopathy, naturopathy, herbal medicine and meditation. There are differences in the diversity of these treatment methods as well as their benefits[13] A study conducted in our country states that there is a lot of news about supplementary methods that can be used to protect against COVID-19 in the written and visual media.[2-6,9-12]

This study was conducted to reveal which type of supplementary people used against COVID-19 disease and determine their behaviours/ideas related to the disease.

MATERIALS AND METHODS

Ethical Considerations: Before initiating the study, ethics committee approval was obtained from Artvin Çoruh University Ethics Committee (Date:06/02/2021, decision no: E-18457941-050.99-4985). The study was carried out following the principles of the Declaration of Helsinki.

Study Design: In the online study, the participants were requested to read the part providing information about the study before completing the questionnaire form and then proceed to the questions. This study is a cross-sectional was conducted between April 1 and May 31, 2021. It was limited to people over the age of 18, and the snowball sampling method was used along with a questionnaire form. The criteria for inclusion in the study are that people who will participate in the study come on a voluntary basis and use a smartphone. The first parts of the snowball ring are the people the researchers can reach on social media, their friends, colleagues and students. This method was preferred because more people can be reached. The questionnaire form created with Google Forms was shared via social media, such as Facebook and WhatsApp. Information about the study was given in the questionnaire form sent. Those who wanted to participate gave their consent and filled out the form. Six hundred fifty-three people completed the questionnaire form between the specified dates.

Limitations of the Study: The snowball sampling method has some negative aspects in terms of reaching the desired entire population. However, this method was preferred because the pandemic was continuing at the time the study was conducted, and more people could be reached. There are limitations in generalizing the research results of online forms to the universe.

Tools: The survey form was created by the researchers by scanning the relevant literature.[2-6, 9-12] The questionnaire form consists of two parts. The first part of the questionnaire consists of 9 questions related to sociodemographic information. In the sociodemographic characteristics form, age, gender, educational status, occupation, work year and status, marital status, number of children, and catching COVID-19 were questioned.

The second part of the questionnaire form consists of 13 questions that address feelings and behaviours related to COVID-19 disease and the use of supplementary medicines and nutrients. The form of supplementary medicine and nutrient use during the COVID-19 pandemic consists of three parts. The first 'feelings' part includes the reasons for fearing the disease. The second 'behaviours' part addresses the measures taken for the disease. The last 'use of supplementary medicines and nutrients' part questions the use of supplementary medicines, supplementary nutrients/vitamins/minerals/teas and herbal teas.

Statistical Analysis: The research data were analyzed using SPSS 22.0 statistical packaged software.

The relationship between the participants' uses of supplementary medicines and nutrients during the COVID-19 pandemic and their ages, educational status, occupation, employment status, work experience, number of children, and status of catching COVID-19 was evaluated. Percentage and frequency distributions were used to determine the participants' descriptive characteristics and uses of supplementary medicines and nutrients during the COVID-19 pandemic. Pearson's chi-squared, Fisher-Freeman-Halton, and Fisher's exact tests were used to compare some sociodemographic characteristics and the use of medicines or supplementary nutrients during the COVID-19 pandemic. Statistical significance accepted $p<0.05$.

RESULTS

Of the individuals participating in the study, 74.4% were in the 18-33 age group, 72.6% were female, 64.6% were single, 65.8% had bachelor's degrees and associate degrees, and 69.8% did not have children. Moreover, 41.5% were students, 49.5% were actively working, and 63.13% had 1-10 years of work experience. Of the participants, 72.1% did not catch COVID-19 (Table 1).

When the participants' emotions and health behaviours towards COVID-19 disease were examined, it was determined that 93.6 per cent were afraid of losing their loved ones, and 91.3 per cent were afraid of infecting their relatives with the disease. 97.9 per cent of the participants wore masks to protect themselves from COVID-19, and 98.5 per cent paid attention to personal hygiene. (Table 2).

Table 1. Socio-demographical characteristics. (n=653).

Variables		n (%)
Age	18-33	486 (74.4)
	34-49	151 (23.1)
	50 and above	16 (2.5)
Gender	Female	474 (72.6)
	Male	179 (27.4)
Marital Status	Single	422 (64.6)
	The married	231 (35.4)
Educational Status	Primary education	18 (2.8)
	High school	73 (11.2)
	Associate-License	430 (65.8)
	Postgraduate	132 (20.2)
Job	Student	271 (41.5)
	Health personnel	114 (17.5)
	Officer/worker	234 (25.8)
	Academician	34 (5.2)
Working Status	Working	339 (51.9)
	Not working	314 (48.1)
Working Year	1-10 year	214 (63.13)
	11-20 years and above	125 (36.87)
Number of children	Has no children	456 (69.8)
	1-2 children	156 (23.9)
	3 children and above	41 (6.3)
COVID-19 Previously Infected	Did not infected	471 (72.1)
	Contacted/isolated	81 (12.4)
	Passed	101 (15.5)

Table 2. Emotions and health behaviours towards COVID-19 disease.

Variables		n (%)
Feelings*	Losing loved ones scares me	611 (93.6)
	Being infected with COVID-19 doesn't scare me,	596 (91.3)
	I'm afraid of getting sick	463 (70.9)
	Increase in stress and anxiety	437 (66.9)
	I'm afraid if I get sick, I will die	258 (39.5)
	Being quarantined scares me	199 (30.5)
Behaviours*	Pay attention to hygiene	643 (98.5)
	Wearing mask	639 (97.9)
	Avoiding crowded places	539 (82.5)
	Keeping the immune system strong	508 (77.8)
	Stay home	504 (77.2)
	Balanced diet	448 (68.6)
	Decreased exercise	445 (68.1)
	Not using public transport	427 (65.4)
	Sports/exercise/walking	276 (42.3)
	Increase the number of meals	260 (39.8)
	Increase in the tendency to use supplements	242 (37.1)
	Do nothing	56 (8.6)

*: More than 1 answer was given to the options.

59.6% of the individuals participating in the research stated that it is possible to protect themselves from COVID-19 with supplementary medicines and herbal supplements, and 37.1% stated that they used medicines or supplements to protect themselves from COVID-19. 32.2% of the individuals participating in the research stated that it is possible to protect against COVID-19 with herbal supplements, and 10.6% stated that they used herbal supplements to protect against COVID-19. (Table 3).

Medicines or supplementary nutrients are used mainly by individuals in the 34-49 age group (51.7%). Participants who use medicines or supplementary nutrients at the highest rates are postgraduates (53.8%) and academicians (61.8%). The groups that use medicines or supplementary nutrients at the highest rates are employed individuals (45.1%) and individuals working for 11-20 years or longer (56%). Medicines or supplementary nutrients are used mainly by individuals (53.8%) with 1-2 children. Individuals with COVID-19 and in isolation (51.5%) are the group that uses medicines or supplementary nutrients the most. (Table 4).

Table 3. Distribution of supplementary medicines and herbal supplements used in the COVID-19 pandemic.

Variables		n (%)
Use of supplements*	Antiviral medicines	177 (27.1)
	Paracetamol	169 (25.9)
	Flu medicine	134 (20.5)
	Aspirin	104 (15.9)
	Ibuprofen	84 (12.9)
Use of supplements/vitamins/ minerals/tea*	Vitamin C	303 (46.4)
	Vitamin D	279 (42.7)
	vitamin B	177 (27.1)
	Iron mineral	165 (25.3)
	Omega-3	142 (21.7)
	Zinc mineral	120 (18.4)
	Vitamin A	116 (17.8)
	Vitamin E	113 (17.3)
	Vitamin-mineral complex	100 (15.3)
	Pre-biotic	96 (14.7)
	Magnesium mineral	91 (13.9)
	Selenium mineral	41 (6.3)
	Copper mineral	37 (5.7)
	Pickle	7 (1.1)
	Propolis	7 (1.1)
	Green tea	22 (3.4)
	Honey	14 (2.1)
	Thyme	13 (2.0)
	Ginger	13 (2.0)
	Linden	11 (1.7)
	Lemon	11 (1.7)
	Spiced teas	11 (1.7)
	Turmeric	7 (1.1)
	Fruit tea	4 (0.6)

*: More than 1 answer was given to the options.

Table 4. Comparison of some sociodemographic characteristics and the situations of using medicines or supplements in the COVID-19 pandemic.

Demographic Information		Uses n (%)	Not Using n (%)	χ^2 and p values
Age	18-33	157 (32.3)	329 (67.7)	χ^2=18.81 p<0.001
	34-49	78 (51.7)	73 (48.3)	
	50 and above	7 (43.8)	9 (56.3)	
Educational Status	Primary and secondary school	7 (38.9)	11 (61.1)	χ^2=20.19 p<0.001
	High school	23 (31.5)	50 (68.5)	
	Associate and license	141 (32.8)	289 (67.2)	
	Graduate	71 (53.8)	61 (46.2)	
Job	Student	75 (27.7)	196 (72.3)	χ^2=26.43 p<0.001
	Health personnel	56 (49.1)	58 (50.9)	
	Officer/Worker	90 (38.5)	144 (61.5)	
	Academician	21 (61.8)	13 (38.2)	
	Working	153 (45.1)	186 (54.9)	χ^2=19.70 p<0.001
	Not working	89 (23.39	225 (71.7)	

Table 4. Continue.

Working Experience	Never worked	89 (28.3)	225 (71.7)	χ^2=29.72 p<0.001
	1-10 years	83 (38.8)	131 (61.2)	
	11-20 years and above	70 (56)	55 (44)	
Number of children	Has no children	142 (31.1)	314 (68.9)	χ^2=25.76 p<0.001
	1-2 children	84 (53.8)	72 (46.2)	
	3 children and above	16 (39)	25 (61)	
COVID -19 Passing Status	I didn't pass	154 (32.7)	317 (67.3)	χ^2=14.74 p=0.001
	I've been contact-isolated	36 (44.4)	45 (55.6)	
	I've been through and isolated	52 (51.5)	49 (48.5)	

DISCUSSION AND CONCLUSION

This study shows the results of using supplementary medicines and nutrients during the COVID-19 pandemic.

The majority of the participants stated that it was possible to protect themselves against COVID-19 with medicines and supplementary nutrients and used medicines or supplementary nutrients for protection. In many studies conducted in our country and worldwide, the use of medicines and nutrients during COVID-19 is mentioned.[15-19] In a study conducted on students in Türkiye, the medicine and nutrient usage rate was high and similar to our study.[12]

Almost all the participants in our study expressed that they feared transmitting the disease to others and losing their loved ones. Furthermore, the majority of the participants stated that there was an increase in their stress and anxiety states. In a study on COVID-19 and fear of death in Spain, similar results were observed.[20] In similar studies, many people stated that they experienced stress, fear of death, and fear of losing their loved ones due to the pandemic.[16,21] Considering the behaviours exhibited for protection against COVID-19, almost all the participants stated that they wore masks and paid attention to hygiene. The vast majority reported that they did not enter crowded places, kept their immune systems strong, did not leave the house and did not use public transportation. A study investigating the behaviours exhibited for protection against COVID-19 in Bangladesh fully coincides with our study.[22] In a similar study, the same results were observed.[6]

Many studies have proven that a strong immune system is required for protection against COVID-19.[9,14,23,24] Many studies emphasize that balanced nutrition[10,13,14,17,23] and healthy living are quite important for a strong immune system.[14,16,23] Trace elements such as vitamins A, B, C, D, E, zinc, iron, selenium, magnesium, and copper play important and complementary roles in supporting the innate and acquired immune system. Deficiencies adversely affect the immune function and may reduce resistance to infections.[10,20-16-19] In our study, the rate of individuals who used the vitamins and minerals mentioned was higher than the rate of individuals who did not use them and said they could consider using them. These data are consistent with the literature and support our study.

In our study, the rates of using vitamins D and C were significantly higher compared to other vitamins. In studies, loading doses of vitamin D are recommended to be taken since they reduce the risk and severity of COVID-19 and protect against acute respiratory tract infection.[23,30-32] The importance of vitamin C in both preventing viral infections and strengthening the immune system is indisputable.[18]

As with all viral infections, data from SARS and influenza indicate that it is more beneficial to start antiviral treatment early. Therefore, it is recommended to start antiviral medications as early as possible.[29,30] In this study, the use of antiviral medication was found to be statistically significantly higher in participants using supplements and nutritional supplements compared to non-users. Other medications used are ibuprofen, paracetamol and aspirin. In a study examining medicines that are likely to be beneficial to COVID-19 patients, ibuprofen was seen to give promising results.[30] In a study examining the medicines used by patients with COVID-19, paracetamol was the most used medicine.[22]

When many medicinal herbs were analyzed for the treatment of COVID-19 patients, it was revealed that medicinal herbs gave good results before the onset of the disease or in the initial phase when there were mild symptoms.[19] In a similar study, about half of the participants benefited from medicinal herbs. A mixture of medicinal herbs such as chamomile, thyme, ginger, mint, cinnamon, fennel, apple cider vinegar and honey.[15] In another study, a majority of the participants stated that you can consume tea, ginger, black cumin, honey and cloves to reduce the risk of COVID-19 infection.[16,22] The results of our study are similar to other studies. This shows that herbal products are of great importance in people's efforts to protect themselves from COVID-19.

In this study, individuals between the ages of 42-49, individuals with postgraduate education and individuals who were sick and isolated used supplementary

medicines and nutrients at more significant rates. In a similar study, individuals aged 60 years and above and individuals who were extremely scared of the pandemic were found to be more likely to take preventive medicines. In the same study, participants with master's degrees consumed protective herbal foods/products more than others.[22] As a result of another study, individuals aged 40 years and above and individuals with higher education were observed to be more likely to use traditional and supplementary. Individuals with higher education were seen to apply self-medication more than individuals with lower levels of education.[11] These results indicate that advancing age and education or experience make people more cautious.

In conclusion, individuals used supplementary medicines and nutrients to protect themselves from COVID-19 with the fear of losing their loved ones rather than their own lives. Many studies have revealed that having a strong immune system, balanced nutrition, and healthy living are extremely important for protection against COVID-19. Due to this situation, people insensibly gravitate toward using vitamins, minerals, and herbal supplements. To prevent this insensible gravitation, further research and information studies are needed.

Ethics Committee Approval: The study was approved by Artvin Çoruh University Non-Interventional Clinical Research Ethics Committee (Date:06/02/2021, Decision No: E-18457941-050.99 -4985).

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

Author Contributions: Concept − UK, BCD; Supervision − UK, BCD; Materials – UK; Data Collection and/or Processing − UK, BCD; Analysis and/or Interpretation − UK, BCD; Writing − UK, BCD.

Peer-review: Externally peer-reviewed.

Acknowledgements: Our study was presented as an oral presentation at the 1st International Nursing Studies Congress held on 12-14 July 2023.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):202-208 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):202-208*

Association of Hemogram Parameters with Body Mass Index in Knee Osteoarthritis

Diz Osteoartritinde Hemogram Parametrelerinin Vücut Kitle İndeksi ile İlişkisi

[1]Koksal GUNDOGDU, [2]Gulsah GUNDOGDU, [3]Alper KURTOGLU

[1]Department of Orthopaedics and Traumatology, Denizli State Hospital, Denizli, Türkiye
[2]Department of Physiology, Pamukkale University Faculty of Medicine, Denizli, Türkiye
[3]Department of Orthopedics and Traumatology, Sakarya University Training and Research Hospital, Sakarya, Türkiye

Koksal Gundogdu: https://orcid.org/0000-0001-6820-5625
Gulsah Gundogdu: https://orcid.org/0000-0002-9924-5176
Alper Kurtoglu: https://orcid.org/0000-0001-9890-1330

ABSTRACT

Objective: This study aims to investigate the relationship between hemogram parameters, which are low-cost, easy, routinely applied low-grade inflammation indicators, and severity of knee osteoarthritis (KOA) and obesity.

Materials and Methods: This study involved 140 KOA patients aged 45 to 85 who underwent knee radiographs, weight and height measurements, and routine laboratory tests. Recorded data included demographic information (gender, age), body mass index (BMI), routine hemogram, and laboratory parameters. Patients were categorized into two groups based on their Kellgren-Lawrence (KL) scores (mild: KL 1-3, severe: KL 4) and four groups according to their BMI (BMI <25, BMI = 25-30, BMI = 30-35, BMI >35).

Results: The findings revealed significantly elevated levels of serum Neutrophil-to-Lymphocyte Ratio (NLR) and C-reactive protein (CRP) in severe KOA compared to mild KOA (P<0.05). Evaluation by BMI demonstrated a statistically significant increase in serum NLR and Neutrophil-to-monocyte Ratio (NMR) in patients with BMI>30 in mild KOA groups, while mean blood NLR was notably higher in patients with BMI=30-35 in severe KOA groups.

Conclusions: These results suggest that NLR and NMR could provide a new perspective on the relationship between obesity and mild KOA in clinical practice, presenting a cost-effective and easily applicable alternative for determining disease prognosis and progression.

Keywords: Knee osteoarthritis, neutrophil/lymphocyte ratio, neutrophil monocyte ratio

ÖZ

Amaç: Bu çalışmada, düşük maliyetli, kolay, rutin olarak uygulanan düşük dereceli inflamasyon göstergeleri olan hemogram parametreleri ile obezite ve diz osteoartriti (DOA) şiddeti arasındaki ilişkinin araştırılması amaçlanmıştır.

Materyal ve Metot: Bu çalışmaya, diz grafileri, kilo ve boy ölçümleri ve rutin laboratuvar testleri yapılmış 45-85 yaş arası 140 KOA hastası dahil edilmiştir. Kaydedilen veriler demografik bilgileri (cinsiyet, yaş), vücut kitle indeksini (BMI), rutin hemogramı ve laboratuvar parametrelerini içeriyordu. Hastalar Kellgren-Lawrence (KL) skorlarına göre iki gruba (hafif: KL 1-3, şiddetli: KL 4) ve BMI'larına göre dört gruba (BMI<25, BMI=25-30, BMI=30-35, BMI>35) ayrılmıştır.

Bulgular: Bu çalışmada, serum CRP ve NLR değerleri şiddetli DOA hastalarında hafif DOA hastalarına kıyasla anlamlı derecede yüksek bulunmuştur (P<0,05). VKİ'ye göre değerlendirildiğinde, kan nötrofil lenfosit (NLR) ve nötrofil monosit (NMR) oranları hafif DOA gruplarında VKİ>30 olan hastalarda istatistiksel olarak anlamlı şekilde artmıştır. Ayrıca, şiddetli DOA gruplarında ortalama kan NLR değeri VKİ=30-35 olan hastalarda diğer gruplara kıyasla anlamlı derecede yüksek bulunmuştur.

Sonuç: Bu sonuçlar, NLR ve NMR'nin klinik ortamda obezite ve hafif DOA arasındaki ilişkiye yeni bir bakış açısı sağlayabileceğini göstermektedir. Bu parametrelerin düşük maliyetli ve kolay uygulanabilmesi, hastalığın prognozunu ve seyrini belirlemede alternatif olabilir.

Anahtar Kelimeler: Diz osteoartriti, nötrofil/lenfosit oranı, nötrofil/monosit oranı

Sorumlu Yazar / Corresponding Author:
Koksal GUNDOGDU,
Department of Orthopedics and Traumatology, Denizli State Hospital, Denizli, Türkiye
Tel: +905079248395
E-mail: koksal_gundogdu@hotmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 08/01/2024
Kabul Tarihi/ Accepted: 09/07/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Gundogdu K and et al. Association of Hemogram Parameters with Body Mass Index in Knee Osteoarthritis. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):202-208. doi: 10.26453/otjhs.1410851

INTRODUCTION

Osteoarthritis (OA) is a complex, chronic, degenerative joint disease characterized by the destruction of articular cartilage and disruption of normal bone formation and breakdown processes. Knee osteoarthritis (KOA) is the most prevalent form of OA.[1] OA develops by combining processes within the subchondral bone, including erosion, sclerosis, osteophytes, subchondral cysts, and synovial inflammation. However, the pathophysiology of OA is still poorly understood.[2]

The main risk factors for KOA are age, obesity, gender, and inflammation.[3] According to the World Health Organization (WHO), obesity is the abnormal or excessive accumulation of fat associated with poor health. According to this calculation, a body mass index (BMI) greater than 30 is considered obese.[4] Physical inactivity, poor eating habits, and genetic factors are commonly associated with obesity.[5] Recently, obesity has been recognized as a major risk factor for KOA and is considered a low-grade inflammatory disease.[6] Abnormal mechanical loading of joints in obesity leads to changes in the composition of the cartilage matrix and joint degeneration, impacting joint biomechanics.[7] However, recent epidemiological data suggest that obese people have about twice the risk of hand OA as normal-weight people, suggesting a more complex relationship.[8] The assessment of KOA is usually based on clinical and radiological findings. The most commonly used radiographic measure of disease severity is the Kellgren-Lawrence (KL) grade.[9] In recent years, as the disease can be diagnosed by pathological findings, new biomarkers and parameters have been emphasized for disease diagnosis and treatment.[10]

OA was considered a noninflammatory disease. However, recent studies have shown that inflammation is a risk factor for both progressive cartilage destruction and symptoms, including joint pain, palpable joint swelling, synovial edema, and osteoarthritis.[11] Complete blood count (CBC) analyses, known for their cost-effectiveness and rapid results, play a crucial role in assessing various diseases. Hemogram parameters such as the platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), and neutrophil/monocyte ratio (NMR), along with biochemical markers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), have emerged as systemic inflammation indicators across various diseases.[12-16]

Inflammation is an important risk factor for both OA and obesity. Therefore, the purpose of this retrospective study is to determine the relationship between hemogram and biochemical parameters, which are low-cost, easy, routinely applied low-grade inflammation indicators, and severity of disease and obesity, as an alternative to showing the prognosis and course of the disease.

MATERIALS AND METHODS

Ethical Considerations: This study was approved by the Ethics Committee of the Medical Faculty of Atatürk University (Date: 30.11.2017, decision no: B.30.2.ATA.0.01.00/91). The study was conducted in accordance with the Helsinki Declaration of 1975, which was revised in 2000.

Participants: For the study, the KOA patients who had been evaluated between August 2016 and December 2017 in the orthopedics and traumatology polyclinic of Erzurum Regional Training and Research Hospital were retrospectively screened by the orthopedic traumatologist. All patients were diagnosed with KOA using the American College of Rheumatology clinical criteria.[17] Patients with autoimmune disorders, post-infectious or post-traumatic arthropathies, systemic inflammation or infection, active malignancy, cardiovascular disease, renal disease, chronic liver disease, and a history of blood transfusion within the previous three months were excluded from the study. According to the hospital software records, 200 patients with KOA diagnosis were screened. One hundred forty patients with knee x-rays, age 45-85 years, weight and height measurements and routine laboratory examinations were included in the study. Demographic data (gender, age) and BMI of KOA patients were determined. Knee radiographs were taken and radiologically graded according to the KL scoring system.[9] This score is based on four radiographic characteristics: joint space narrowing, osteophytes, subchondral cysts, and subchondral sclerosis. Patients were divided into two groups by KL grade: patients with KL grade 1-3 (mild) and patients with KL grade 4 (severe). The patients were also divided into four groups according to BMI: patients with BMI > 35, patients with BMI = 30-35, patients with BMI = 25-30 and patients with BMI < 25.

Laboratory: The laboratory results of the patients were examined. ESR and CRP were obtained from biochemical analyses. White blood cell (WBC), lymphocyte, neutrophil, thrombocyte, and monocyte counts were obtained from the hemogram. Blood NLR, PLR, and NMR levels were calculated. NLR was calculated by dividing neutrophil count by lymphocyte count, PLR by thrombocyte count by lymphocyte count and NMR by neutrophil count by monocyte count. Laboratory and radiological evaluation data were obtained from the same patient.

Statistical Analysis: All statistical analyses were performed using SPSS software version 20. Results were presented as mean±standard deviations for age,

BMI, hemogram and biochemical parameters. Statistical comparison of laboratory parameters levels from mild and severe KOA was used in Independent -Samples T tests. According to BMI, statistical comparison of laboratory parameters levels of groups was used the Kruskal Wallis test and Pairwise comparisons were performed using the Mann-Whitney U test. Statistical significance was defined as a P value < 0.05.

RESULTS

A retrospective analysis encompassed 140 patients stratified into two groups based on the severity of KOA: mild KOA and severe KOA. The comparative assessment of demographic and laboratory parameters, as illustrated in Table 1, revealed noteworthy distinctions between the two groups. Patients with severe KOA exhibited significantly higher mean age (P=0.001), mean CRP (P=0.009), mean neutrophil count (P=0.044), and mean blood NLR (P=0.036) compared to those with mild OA. However, the observed variations in mean ESR, mean WBC, mean PLR and mean NMR did not reach statistical significance. These findings underscore the relevance of age, CRP levels, neutrophil count, and blood NLR in distinguishing the severity of KOA within the studied patient cohort (Table 1).

A cohort of 50 patients diagnosed with mild KOA underwent a comprehensive evaluation, with particular attention given to BMI categorization. The patients were grouped into four BMI categories: BMI<25, BMI=25-30, BMI=30-35, and BMI>35. The comparative analysis of demographic and laboratory parameters across these BMI groups is detailed in Table 2. Notably, patients with BMI=30-35 and BMI>35 exhibited a significant increase in mean blood NLR compared to those with BMI=25-30. Similarly, mean blood NMR showed a noteworthy elevation in patients with BMI=30-35 and BMI>35 compared to those with BMI<25 and BMI=25-30. However, other parameters did not display statistically significant differences among the four BMI groups (Table 2).

Table 1. Comparison of mild and severe KOA in terms of demographics and laboratory parameters.

Parameters	Mild KOA (n=50)	Severe KOA (n=90)	p[a]
Age	60.840 ± 7.527	65.511 ± 7.527	0.001*
BMI	32.019 ± 8.956	31.344 ± 5.371	0.497
WBC	7.478 ± 1.871	8.226 ± 2.576	0.073
CRP, (mg/dL)	0.506 ± 0.531	1.983 ± 3.893	0.009*
ESR, (mm/h)	13.220 ± 8.330	16.766 ± 12.257	0.070
Neutrophil count, (K/uL)	4.678 ± 1.541	5.377 ± 2.143	0.044*
Lymphocyte count, (K/uL)	2.359 ± 0.712	2.191 ± 0.806	0.221
Thrombocyte count, (K/uL)	300.41 ± 87.968	289.233 ± 86.760	0.493
Monocyte count, (K /uL)	0.498 ± 0.165	0.522 ± 0.207	0.469
NLR	2.222 ± 1.291	2.777 ± 1.578	0.036*
PLR	137.480 ± 58.822	146.362 ± 71.385	0.455
NMR	10.134 ± 4.370	11.025 ± 4.668	0.271

Results are given in mean ±SD; [a]: Independent-Samples T tests; *:P-value of <0.05 was considered to be significant; BMI: body mass index; WBC: White blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR:neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; NMR: neutrophil/monocyte ratio.

Table 2. According to BMI, comparing demographic and laboratory parameters in mild KOA.

Parameters	Mild KOA (n=50)				
	BMI <25	BMI =25-30	BMI =30-35	BMI >35	p[a]
Age	62.7±10.9	58.7±8.3	61.3±9.8	61.5±8.4	0.895
WBC	7.5±1.02	7.4±1.4	7.1±2.4	7.6±2.1	0.277
CRP, (mg/dL)	0.36±0.05	0.36±0.09	0.55±0.38	0.65±0.8	0.110
ESR, (mm/h)	9.7±5.5	13.4±10.2	15.6±7.5	13.3±8.0	0.588
Neutrophil count, (K/uL)	4.62±1.27	4.12±1.02	4.46±2.13	5.27±1.5	0.165
Lymphocyte count, (K/uL)	2.3±0.76	2.76±0.68	2±0.47	2.21±0.7	**0.027**[*4,5]
Thrombocyte count, (K/uL)	313±79	316±60	245±34	308±119	**0.023**[*2,4]
Monocyte count, (K/uL)	0.59±0.13	0.55±0.16	0.39±0.08	0.46±0.1	**0.014**[*2,3,4]
NLR	2.32±1.31	1.57±0.57	2.59±2.27	2.52±0.9	**0.027**[*4,5]
PLR	151±63	119±31	129±42	150±77	0.422
NMR	8.21±4.37	7.85±2.36	11.7±6.22	12.07±4	**0.002**[*2,3,4,5]

Results are given in mean ±SD; [a]: The Kruskal-Wallis test was used for the comparison of the groups; For pairwise comparisons, the Mann-Whitney U test was used; *: P value of <0.05 was considered significant; Pairwise comparisons of groups [1]: BMI <25 vs BMI 25-30; [2]BMI <25 vs BMI 30-35; [3]: BMI <25 vs BMI >35; [4]: BMI 25-30 vs BMI 30-35; [5]: BMI 25-30 vs BMI>35; [6]: BMI 30-35 vs BMI>35; BMI: body mass index; WBC: White blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR:neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; NMR: neutrophil/monocyte ratio.

Concurrently, a cohort of 90 patients diagnosed with severe KOA underwent a parallel evaluation, with BMI stratification into four groups: BMI <25, BMI = 25-30, BMI = 30-35, and BMI >35. The comparative analysis of demographic and laboratory parameters across these BMI groups is presented in Table 3. A statistically significant difference was observed in mean age across all four BMI groups. Additionally, mean blood NLR exhibited a significant increase in patients with BMI =30-35 compared to other groups, and a similar tendency was noted for patients with BMI >35 compared to those with BMI < 25. However, no statistically significant differences were identified among the four groups for other parameters (Table 3).

Table 3. According to BMI, comparing demographic and laboratory parameters in severe KOA.

Parameters	Severe Knee OA (n=90)				
	BMI <25	**BMI =25-30**	**BMI =30-35**	**BMI >35**	**p[a]**
Age	70.6±7.1	68.1±5.5	62.6±7.4	63.5±7.6	**0.002**[*2,3,4,5]
WBC	7.8±2.03	8.1±2.7	8.2±2.7	8.5±2.5	0.938
CRP, (mg/dL)	1.04±1.1	2.24±4.1	2.24±4.8	1.8±2.8	0.727
ESR, (mm/h)	14±11.4	16±10.8	17.2±14	18±11.9	0.706
Neutrophil count, (K/uL)	5.1±2.08	5.56±2.3	5.95±2.1	6.01±1.8	0.186
Lymphocyte count, (K/uL)	1.96±0.8	1.98±0.8	2.48±0.7	2.11±0.6	**0.021**[*2,4]
Thrombocyte count, (K/uL)	293±106	264±76	295±87	380±82	0.353
Monocyte count, (K/uL)	0.46±0.1	0.51±0.2	0.52±0.2	0.56±0.1	0.147
NLR	3.05±1.6	3.08±1.5	4.12±0.9	3.51±2.1	**0.017**[*2,3,4]
PLR	165±73	143±47	135±91	155±54	0.061
NMR	11.4±4.8	11.4±4.3	10.5±5.2	10.9±4	0.488

Results are given in mean ±SD; [a]: The Kruskal-Wallis test was used for the comparison of the groups; For pairwise comparisons, the Mann-Whitney U test was used; *: P value of <0.05 was considered significant. (Pairwise comparisons of groups; [1]: BMI <25 vs BMI 25-30; [2]: BMI <25 vs BMI 30-35; [3]: BMI <25 vs BMI >35, [4]: BMI 25-30 vs BMI 30-35, [5]: BMI 25-30 vs BMI>35; BMI: body mass index; WBC: White blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; NMR: neutrophil/monocyte ratio).

DISCUSSION AND CONCLUSION

In this study, we hypothesized that routine hemogram and biochemical inflammatory parameters in patients with KOA were associated with the BMI of patients. In this study, according to the severity of the disease, we found that blood CRP and NLR levels statistically significantly increased in the severe KOA group compared to the mild KOA group; there were no significant differences in the other parameters between the two groups. Additionally, according to the BMI of patients, there was no significant difference in any of the parameters among the four groups. However, blood NLR, and NMR levels statistically significantly increased in patients with BMI>30 in the mild KOA group.

OA is a progressive condition affecting joints and surrounding tissues, marked by cartilage degradation and alterations in the subchondral bone. As its frequency rises, OA has grown to be a significant health issue. With the rise in obesity and the aging population, there have been no laboratory results linked to OA in recent years, which has become a significant issue. Because of this, researchers are now concentrating on the availability of novel biomarkers for the early diagnosis of the illness. Although OA has always been described as a noninflammatory disease, new research indicates that low-grade inflammation may be involved in the pathogenesis of the condition.[1,2,10]

KOA is a common form of OA characterized by the degradation of cartilage tissue and joint structures. It is also associated with changes in the subchondral bone.[1] KOA results in muscle stiffness. It has an impact on quality of life and physical activity. Furthermore, it is linked to a considerable financial burden concerning the costs associated with its treatment. Obesity is associated with many comorbidities, encompassing cardiovascular disease, type 2 diabetes, high blood pressure, OA and cancer. Obesity is a common metabolic disease that is a major cause of morbidity and mortality.[18] Low-grade systemic inflammation is known to result from obesity. Excess weight can lead to joint destruction due to mechanical stress on the joints. This is the cause of OA. The pathogenic features of obesity and OA are the same: As obesity develops, the risk of OA increases, and inflammation may play a role in this connection.[6] Being overweight puts an increased strain on the joints, which can lead to stress and the breakdown of the cartilage, resulting in OA. Weight loss was shown to significantly improve KOA symptoms by Christensen et al.[19] In the study by Peker et al., which involved only female patients, body composition analysis based on bioelectrical impedance analysis was conducted on patients with obesity and KOA. It was found that patients with

gonarthrosis had higher percentages of body fat and leg fat mass, while their lean mass was lower. The study concluded that in individuals with obesity and gonarthrosis, weight loss should primarily target fat tissue.[20] According to a recent study, obese people were about twice as likely to have hand OA as people of average weight.[8] These findings suggest that there may be a link between obesity and OA. The link between obesity and increased systemic inflammation has been well-documented, with studies showing that obesity is associated with elevated inflammatory markers such as CRP and NLR. Our study supports this connection by demonstrating increased NLR and NMR levels in obese patients (BMI > 30) with mild KOA. This is consistent with previous research highlighting the inflammatory role of obesity.

WBC counts and subtypes have been suggested as biological markers of inflammation in several diseases. These markers, which can be obtained without easily adding economic burden to hemogram, have gained importance in many diseases such as cardiovascular diseases, end-stage renal disease, cerebrovascular diseases, and inflammatory diseases. Meanwhile, many studies have shown NLR, PLR and NMR levels to indicate systemic inflammation.[12-16]

Recently, routine hemogram parameters, especially in the case of inflammatory diseases, have become the focus of researchers as a marker of inflammation because of the advantage that they can be easily obtained without bringing an additional economic burden. In recent years, PLR has been recognized as an important biomarker to detect inflammation in cardiovascular diseases, many cancers, cerebrovascular diseases and many inflammatory diseases such as COVID-19, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), OA, ulcerative colitis (UC), and Familial Mediterranean Fever (FMF).[21-25] In autoimmune diseases, while platelet count usually increases, lymphocyte count decreases. An increase in the PLR ratio has been found to be associated with disease activity in RA and SLE and disease severity in psoriasis.[23,24] Atar et al. found no significant relationship between OA and PLR, which aligns with our results. This could be due to differences in patient demographics and study designs.[26] Additionally, while Shi et al. found significant increases in PLR among KOA patients compared to controls, they did not find a correlation with disease severity, suggesting potential variability in inflammatory markers.[15] Similarly, Hira et al. found a significant increase in the PLR ratio in patients with OA disease.[27] In another study performed by Tasoglu et al., it was concluded that the PLR ratio is an important indicator of the severity of the disease in hip OA patients.[28] In this study, although an increase in serum PLR level was detected in severe KOA patients compared to mild KOA patients, it did not reach a statistically significant level. At the same time, when we divided the patients according to BMI, no significant increase was detected.

Similar to PLR, NMR is a routine blood test. It can be used as a marker of systemic inflammation in many inflammatory diseases.[11-13] Liu et al. showed for the first time that NMR is effective in differentiating between infected patients without lupus nephritis (LN) and healthy individuals or in differentiating between an infection from a flare in patients with LN.[13] The ability of admission NMR to accurately predict in-hospital mortality in patients with severe COVID-19 was first demonstrated by Rizo-Téllez et al.[14] Shi et al. showed that NMR can be used as a potential marker for the severity of KOA as an independent factor.[15] In this study, an increase in serum NMR level was detected in severe KOA patients compared to mild KOA patients. At the same time, when we divided the patients according to BMI, serum NMR levels statistically significantly increased in patients with BMI>30 in the mild OA groups.

NLR is another routine blood test that can serve as a marker of systemic inflammation in many inflammatory diseases.[21,22,24,25] For example, studies have shown elevated blood NLR levels in patients with active UC compared to control subjects, indicating that NLR can distinguish UC patients from healthy individuals and reflect the state of the intestinal mucosa, especially when colonoscopy is not an option.[25] Additionally, blood NLR levels were found to be higher in RA patients compared to controls and were connected to CRP, ESR, and disease activity. There was also a substantial association between the DAS 28-ESR score and PLR and NLR.[24] Dincer et al.'s study further highlighted the utility of blood NLR levels as an indicator of subclinical inflammation in patients with FMF.[21] Tasoglu et al.'s pioneering work in the literature identified blood NLR levels as a novel and promising marker for inflammation, particularly serving as an indicator of KOA severity.[29] Supporting the inflammatory hypothesis in OA pathogenesis, another study demonstrated higher blood NLR levels in the OA group compared to the control group. The observed increase in CRP and NLR levels in severe KOA patients may be attributed to chronic inflammation's impact on joint tissues. Chronic inflammation can lead to cartilage degradation and changes in the subchondral bone, which are characteristic features of KOA. In our previous study, we found that although the mean blood NLR was significantly elevated in KL grade 4 compared with the other grades, there was no statistical difference between patients with KOA and healthy controls.[30] Similarly, in our previous study, we found that blood NLR levels statistically signifi-

cantly increased in the severe KOA group compared to the mild KOA group, and we also found that blood NLR levels statistically significantly increased in patients with BMI>30 in the mild KOA group. Our findings support the emerging view that low-grade systemic inflammation is involved in the pathogenesis of OA, challenging the traditional view of OA as a purely non-inflammatory condition. This aligns with the broader theoretical framework linking obesity, inflammation, and metabolic disorders with chronic diseases like OA. Based on our findings, we propose a model where systemic inflammation acts as a mediator between obesity and KOA severity. In this model, inflammatory markers such as NLR and NMR can serve as indicators of disease progression and severity, providing a basis for early intervention and personalized treatment strategies.

The most significant limitation of our study is the relatively small sample size for KOA, which has become a significant health problem in recent years. The single-center design also limits the generalizability of our findings. Therefore, our results should be supported by prospective studies with larger patient populations and histological research.

In conclusion, despite some limitations, our study has shown that NLR and NMR ratios may be low-cost laboratory tests that can be used as markers in obesity-related KOA. The data obtained from this study suggest that NLR and NMR could provide a new perspective on the relationship between obesity and mild KOA in clinical settings. Future research should focus on larger, multicenter studies to validate these findings and explore the underlying mechanisms in more detail.

Ethics Committee Approval: Our study was approved by the Atatürk University Ethics Committee (Date: 30.11.2017, Decision no: B.30.2.ATA.0.01.00/91). The study was conducted in accordance with the Helsinki Declaration of 1975, which was revised in 2000.

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

Author Contributions: Concept – KG, GG; Supervision – KG, GG; Materials – KG; Data Collection and/or Processing KG; Analysis and/or Interpretation – KG, GG; Writing – KG, GG, AK.

Peer-review: Externally peer-reviewed.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):209-215 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):209-215*

The Role of Troponin Measured on Admission to the Emergency Department in Patients with Acute Ischemic Stroke to Predict Stroke Severity and Neurological Outcome

Akut İskemik İnme Hastalarında Acil Servise Başvuru Sırasında Ölçülen Troponinin İnme Şiddetini ve Nörolojik Sonuçları Öngörmedeki Rolü

[1]Seda YILMAZ, [1]Gülşah ÇIKRIKÇI IŞIK, [2]Fatmanur KARAARSLAN, [1]Şeref Kerem ÇORBACIOĞLU, [3]Osman KORUCU, [1]Yunsur ÇEVİK

[1]Department of Emergency Medicine, University of Health Sciences Atatürk Sanatorium Training and Research Hospital, Ankara, Türkiye
[2]Soma Public Hospital, Manisa, Türkiye
[3]Department of Neurology, University of Health Sciences Atatürk Sanatorium Training and Research Hospital, Ankara, Türkiye

Seda Yılmaz: https://orcid.org/ 0000-0003-0579-1545
Gülşah Çıkrıkçı Işık: https://orcid.org/0000-0002-6067-7051
Fatmanur Karaaslan: https://orcid.org/ 0000-0003-4465-9598
Şeref Kerem Çorbacıoğlu: https://orcid.org/0000-0001-7802-8087
Osman Korucu: https://orcid.org/0000-0001-6354-3297
Yunsur Çevik: https://orcid.org/0000-0003-1325-0909

ABSTRACT

Objective: This study aims to investigate the prognostic value of cardiac troponin levels measured at admission to the emergency department (ED) for stroke severity assessed by the National Institutes of Health Stroke Scale (NIHSS) and neurological outcomes determined by Modified Rankin Scale (mRS) scores in patients diagnosed with acute ischemic stroke (AIS).

Materials and Methods: Patients presenting to ED with a diagnosis of AIS confirmed by neuroimaging findings were included. Patients were divided into 2 groups based on troponin-I levels: elevated and normal. NIHSS during admission, 30-day all-cause mortality data, and 30-day mRS were examined. In comparisons between groups, categorical variables were evaluated with Chi-square and continuous variables were evaluated with the Mann-Whitney-U test. To determine the prognostic value of troponin with poor outcomes in stroke patients, diagnostic 2x2 tables were made.

Results: The study was conducted with 200 patients. Troponin elevation was detected in 37, and mortality was significantly higher in this group. The sensitivity of troponin to predict mortality was 88.89%, and PLR (positive likelihood ratio) was 5.85 (3.89–8.79). The 30-day mRS scores were significantly higher in the elevated troponin group. NIHSS scores didn't show a significant difference between groups.

Conclusions: Troponin levels assessed at admission in AIS patients may be a prognostic marker for mortality and adverse neurological outcomes.

Keywords: Ischemic stroke, mortality, troponin

ÖZ

Amaç: Bu çalışmanın amacı, akut iskemik inme (Aİİ) tanısı alan hastalarda acil servise (AS) başvuru sırasında ölçülen kardiyak troponin düzeylerinin, Ulusal Sağlık Enstitüleri İnme Ölçeği (NIHSS) ile değerlendirilen inme şiddeti ve Modifiye Rankin Ölçeği (mRS) ile belirlenen nörolojik sonlanımı belirlemedeki prognostik değerini araştırmaktır.

Materyal ve Metot: Acil servise Aİİ tanısı ile başvuran ve tanısı nörogörüntüleme bulguları ile doğrulanan hastalar dahil edildi. Hastalar troponin I düzeylerine göre yüksek ve normal olmak üzere iki gruba ayrıldı. Başvuru sırasındaki NIHSS, 30 günlük tüm nedenlere bağlı mortalite verileri ve 30 günlük mRS incelendi. Gruplar arası karşılaştırmalarda kategorik değişkenler Ki-kare ile sürekli değişkenler ise Mann Whitney U testi ile değerlendirildi. Troponinin inme hastalarında kötü sonlanımla prognostik değerini belirlemek için, tanısal 2x2 tablolar yapıldı.

Bulgular: Çalışma 200 hasta ile gerçekleştirildi. Troponin yüksekliği 37 hastada tespit edildi ve bu grupta mortalite anlamlı olarak daha yüksekti. Troponin'in mortaliteyi öngörmedeki duyarlılığı %89, PLR (pozitif olabilirilik testi) 5,85 (3,89–8,79) idi. Troponin yüksekliği olan grupta 30 günlük mRS skorları anlamlı derecede yüksekti. NIHSS skorları gruplar arasında anlamlı bir fark göstermedi.

Sonuç: Aİİ hastalarında başvuru sırasında ölçülen troponin düzeyleri mortalite ve olumsuz nörolojik sonuçlar açısından prognostik bir belirteç olabilir.

Anahtar Kelimeler: İskemik inme, mortalite, troponin

Sorumlu Yazar / Corresponding Author:
Gülşah Çıkrıkçı Işık
University of Health Sciences, Atatürk Sanatorium Training and Research Hospital, Emergency Medicine Department, Ankara / Türkiye
Tel: +90 505 5873436
E-mail: gulsah8676@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 23/01/2024
Kabul Tarihi/ Accepted: 14/08/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Yılmaz S and et al. The Role of Troponin Measured on Admission to the Emergency Department in Patients with Acute Ischemic Stroke to Predict Stroke Severity and Neurological Outcome. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):209-215. doi: 10.26453/otjhs.1424361

INTRODUCTION

Because of the increased availability of reliable biomarkers, the role of the laboratory in the decision-making process has become undeniable in modern clinical practice. Cardiac troponins are one of the most valuable biomarkers, especially the "high-sensitive" ones, widely used for early detection of myocardial infarction.[1] It is a known fact that cardiac troponin levels predict mortality in clinical conditions due to cardiac causes. However, in recent years, it has been shown that troponin levels help to predict mortality in many non-cardiac medical conditions, such as strokes, pulmonary diseases, and sepsis.[2]

Ischemic stroke (IS) remains one of the most common causes of death and the leading cause of disability worldwide; thus, prediction of prognosis is still an important need for IS patients.[3] Recent studies have demonstrated that troponin positivity on admission is an independent predictor of mortality in acute ischemic stroke (AIS).[3,4] Even moderately elevated troponin levels in AIS are associated with in-hospital deaths and unfavourable neurologic outcomes at hospital discharge.[5] The elevation of troponin in IS is believed to be caused by comorbid conditions and cardiac complications; however, in a TRELAS study, it was demonstrated that despite similar baseline troponin levels, coronary culprit lesions were significantly less frequent in IS patients compared with age and sex and matched non-ST elevated acute coronary syndrome patients.[6] Therefore, the exact mechanism of myocardial injury after IS is still unclear, and ongoing studies elucidating hypotheses related to etiology, such as demand ischemia and the overshooting systemic response, are currently being conducted.[7]

Although many studies exist about the relationship between mortality and troponin in IS, there are limited publications on the predictive role of troponin in stroke severity and neurological outcome. This study aims to evaluate the interaction between the neurologic severity of IS patients and troponin levels at emergency department (ED) admission and determine the prognostic role of troponin at admission on mortality and neurological outcome.

MATERIALS AND METHODS

Ethical Committee Approval: Our study was approved by the Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 08.03.2022, decision no: 2012-KAEK-15/2489). The study was conducted following the Helsinki Declaration throughout the research process. The written informed consent form for all participants was obtained.

Study Design and Population: Patients admitted to the Keçiören Training and Research Hospital ED between April 2022 and December 2022 and diagnosed with AIS were consecutively included in the study. The patients were diagnosed with AIS based on their history, neurological examination, radiological findings, and neurology consultation. All the patients with a suspicion of stroke first had cranial CT (computerized tomography), and then, in case of ongoing suspicion, they had diffusion-weighted magnetic resonance imaging (DWMRI). The most common radiologic finding in cranial CT was hypodense lesions and acute diffusion restriction in DWMRI. (A summary of the radiologic findings is given in Table 1). Being older than 40 years of age (since the etiological causes of IS in patients under 40 years of age need to be elucidated) and being neurologically intact before an AIS attack were determined as inclusion criteria. Pregnant patients, patients with kidney failure, those with atrial fibrillation, atrial flutter, and ventricular arrhythmia detected on ECG at the time of admission, patients diagnosed with acute coronary syndrome according to ECG, clinical and laboratory findings on admission, those who had cardiac intervention (angiography, by -pass) in the last 4 weeks, patients who had stroke in last 4 weeks, and those who could not be followed up for 30 days were excluded.

Study Process: The patients' demographic variables, medical history, medications, vital signs, ECG findings, radiological findings, and ED outcomes (discharge, inward admission, intensive care unit admission) were recorded in the study forms. The troponin I levels of the patients were examined from blood samples taken at ED admission with an Abbott Alinity high-sensitive device. Normal levels were defined as <15.6 ng/L for males and <34 ng/L for females, according to the standard reference values.

To understand the clinical severity of the stroke, for all patients diagnosed with AIS in the ED, National Institutes of Health Stroke Scale (NIHSS) scores were calculated. NIHSS is a widely used scale that evaluates different brain functions, such as consciousness, sight, sensation, movement, speech and language, whose score ranges from 0 to 42. NIHSS scores above 16 highly predict mortality and poor neurologic outcomes, and scores lower than 6 predict good outcomes.[8] Since our hospital does not have a stroke center, most of our stroke patients' conditions are mild in severity. Therefore, we determined our group as patients suffering from a mild stroke (NIHSS score ≤4) and others (NIHSS score >4) for diagnostic tests (≤4 is the determined limit for mild stroke according to NIHSS).[9]

We used the Modified Rankin Scale (mRS) to evaluate the patients' neurological outcomes. This scale

contains 7 levels, ranging from 0 (no neurologic symptom) to 6 (dead); scores of 0-1-2 define functional independence, and 3-4-5 categorize patients as functionally dependent.[10] Patients were evaluated on the 30th day after the first admission; this control was done with phone calls to patients or their first-degree relatives. Modified Rankin Scales were calculated, and mRS scores ≥3 were accepted as a poor neurologic outcome.

Outcomes: The study's first aim is to examine the relationship between troponin levels at admission to the ED and the clinical severity of the AIS patients, which the NIHSS determined. The second aim is to examine the relationship between troponin and the patients' 30th-day neurological outcome, which is defined according to the mRS. The study's third aim is to examine the relationship between troponin levels and mortality of AIS patients.

Sample Size and Power Analysis: All consecutive AIS patients who applied to the ED between April 2022 and December 2022 and met the study criteria were included. Out of 280 patients, 80 were excluded due to the exclusion criteria, and statistical analyses were performed on the data of the 200 remaining patients (Figure 1).

Post-hoc power analyses were conducted with the G Power 3.1.9.7 program. For the neurological outcome endpoint, a significant difference was detected between the troponin positive and negative groups (p=0.002) with a 5% type-1 error; the power of the study was calculated as 0.99.

Statistical Analysis: Data analysis was effectuated using SPSS for Windows 22 (IBM, Chicago, USA). After determining whether the data showed a normal distribution using the Kolmogorov–Smirnov test, all data were presented as mean±standard deviation or median value and interquartile difference (IQR: 25–75%). For comparisons between groups, categorical variables were evaluated with the chi-square test, and continuous variables were evaluated with the Mann–Whitney U test. To determine the predictive value of troponin in terms of poor outcome and the severity of the stroke, diagnostic 2 × 2 tables were used. The Spearman correlation test was used to analyze the correlation between troponin levels and NIHSS and mRS. The statistical significance level was accepted as $p<0.05$.

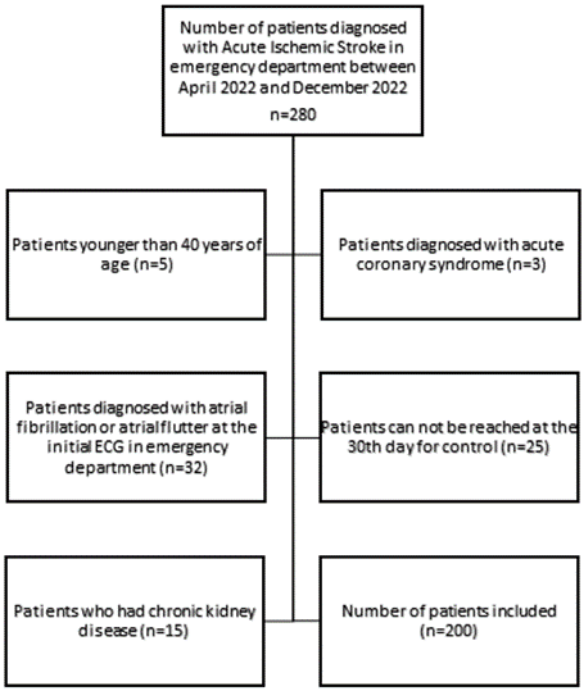

Figure 1. Flow chart.

RESULTS

A total of 200 patients were included in the study with a median age of 68 (IQR: 25–75; 61–76), and 98 of them were female. The most common comorbid conditions were hypertension (66.5%), diabetes mellitus (45%), and coronary artery disease (27%). The median NIHSS score was 2 (IQR: 25–75; 1–4), and the median mRS score was 1 (IQR: 25–75; 0–2). Nine of the patients passed away within 30 days. The median troponin level of all patients was 5.45 ng/mL (IQR: 2.3–18.9); troponin levels were higher than the reference limits in 37 patients. General characteristics, laboratory findings, and the NIHSS and mRS scores of the patients are summarized in Table 1.

Patients were divided into 2 groups: normal troponin (n=163) and high troponin (n=37). Age and sex distributions were similar between the two groups. There was no difference in comorbid conditions, except in heart deficiency, which was higher in the troponin-positive group (p = 0.012). Urea and creatinine levels were higher in the troponin-positive group. NIHSS scores were similar between the groups, but the mRS score was significantly higher in the troponin-positive group (p=0.002). In addition, mortality was significantly higher in the troponin-positive group (p<0.001) (8 vs. 1 patient). Data that shows comparisons between the two groups are given in Table 2.

Table 1. Characteristics and general findings of the study population. (n=200).

Parameters			Data
Demographics		Age, median IQR(25-75)	68 (61–76) years
		Sex Female, n (%)	98 (49)
		Male, n (%)	102 (51)
Comorbidities		Hypertension, n (%)	133 (66.5)
		Diabetes mellitus, n (%)	90 (45)
		Coroner artery disease, n (%)	54 (27)
		Medical history of stroke, n (%)	28 (14)
		Heart failure, n (%)	9 (4.5)
		Other*, n (%)	68 (34)
Radiologic Findings	Cranial CT	No acute pathology	117 (58.5)
		Hypodense lesion	30 (15)
		Other**	53 (26.5)
	Diffusion weighted MRI	Acute diffusion restriction	167 (83.9)
		Hypointense region	2(1)
		Hyperintense region	30 (15.1)
Laboratory findings		Urea, mg/dL, median IQR(25-75)	38 (29–49)
		Creatinine, mg/dL, median IQR(25-75)	0.99 (0.88–1.19)
		Troponin, ng/L, median IQR(25-75)	5.45 (2.3–18.9)
Number of patients with high troponin levels, n (%)			37 (18.5)
30-day mortality, n (%)			9 (4.5)
NIHSS, median IQR(25-75)			2 (1–4)
mRS, median IQR(25-75)			1 (0–2)

*: Chronic obstructive pulmonary disease, asthma, epilepsy, hyperlipidemia, and rheumatism; NIHSS: National Institutes of Health Stroke; Scale; mRS: Modified Rankin Scale; **: Other findings in cranial CT were encephalomalacia, atrophy, meningioma; Abbreviations: CT; computerized tomography, MRI; Magnetic Resonance Imaging.

Table 2. Comparison of demographic and clinical findings between the normal troponin and high troponin groups (variables are given as n (%) or median IQR (25–75)).

Parameters		Normal Troponin n=163	High Troponin n=37	p-value
Demographics	Age, median IQR(25-75)	68 (61–76)	70 (62–77)	0.502
	Sex Female, n (%)	81 (49.7)	17 (45.9)	0.681
	Male, n (%)	82 (50.3)	20 (54.1)	
Comorbidities	Hypertension, n (%)	106 (65)	27 (73)	0.355
	Diabetes mellitus, n (%)	76 (46.6)	14 (37.8)	0.332
	Coroner artery disease, n (%)	41 (25.2)	13 (35.1)	0.217
	Medical history of stroke, n (%)	21 (12.9)	7 (18.9)	0.339
	Heart failure, n (%)	4 (2.5)	5 (13.5)	**0.012**
	Other*, n (%)	56 (34.4)	12 (32.4)	0.824
Laboratory findings	Urea, mg/dL, median IQR(25-75)	37 (28–48)	49 (38–60)	**0.001**
	Creatinine, mg/dL, median IQR(25-75)	0.97 (0.86–1.14)	1.24 (0.99–1.72)	**0.001**
	Troponin, ng/L, median IQR(25-75)	3.8 (1.8–8,6)	69.8 (38–137)	**0.001**
NIHSS, median IQR(25-75)		2 (1–3)	2 (1–4)	0.969
30-day mortality, n (%)		1 (0.6)	8 (21.6)	**0.001**
mRS, median IQR(25-75)		1 (0–2)	1 (1–5)	**0.002**

*: Chronic obstructive pulmonary disease, asthma, epilepsy, hyperlipidemia, and rheumatism; F: Female; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale.

The diagnostic value of troponin in determining stroke severity, defined according to NIHSS, poor outcome according to the mRS, and mortality were investigated. Although a NIHSS value of ≥16 includes moderate and severe stroke groups, since the highest NIHSS value in our current data is 14, the groups were determined as the mild stroke group with a NIHSS value of ≤4 and others. According to this data, the sensitivity of troponin in predicting moderate and more severe strokes was calculated as 19.35%. For the prediction of poor outcomes, troponin sensitivity was 39.47%. In terms of mortality prediction, the sensitivity of troponin was 88.89%, and the specificity was 84.82%. Data about troponin's prognostic value is presented in Table 3. We also analyzed the correlation between troponin and NIHSS, mRS and mortality. There was no correlation between NIHSS and troponin (p=0.053), but between troponin and mRS and troponin and mortality, there was a significant weak positive correlation (p<0.001 for both and r=0.304 and r=0.300, respectively).

Table 3. Prognostic value of troponin.

	Prognostic value of troponin for predicting moderate and more severe stroke based on NIHSS	**Prognostic value of troponin for predicting poor outcome based on mRS**	**Prognostic value of troponin for predicting mortality**
Sensitivity, % (95% CI)	19.35 (7.45–37.47)	39.47 (24.04–56.61)	88.89 (51.75–99.72)
Specificity,% (95% CI)	81.66 (74.99–87.18)	86.42 (80.16–91.29)	84.82 (78.93–89.59)
PLR,% (95% CI)	1.06 (0.48–2.33)	2.91 (1.67–5.06)	5.85 (3.89–8.79)
NLR,% (95% CI)	0.99 (0.82–1.19)	0.7 (0.54–0.91)	0.13 (0.02–0.83)
Accuracy,% (95% CI)	72 (65.23–78.1)	77.5 (71.08–83.09)	85 (79.28–89.64)

DISCUSSION AND CONCLUSION

In this study, we evaluate the relationship between cardiac troponin levels at the admission of IS patients, mortality, and stroke severity determined according to the NIHSS and stroke outcome was determined according to the mRS. We found that troponin has a predictive role in mortality at high sensitivity (89%) and specificity (85%). However, despite a significant troponin increase in the poor outcome group, sensitivity was only 39% in this group. Troponin levels did not differ between the groups in terms of severity.

Cardiac involvement and troponin elevation in IS is a much-needed research initiative, and recent studies supporting the fact that the cardiac consequences of stroke are associated with higher mortality and poor neurological outcomes have been conducted.[11-13] This condition, called stroke-heart syndrome, points to an integrated pathogenesis involving post-stroke neurocardiogenic mechanisms.[14] Autonomic dysfunction, increased inflammation, the effect of local and systemic mediators, and, consequently, changes in cardiomyocyte metabolism are thought to be the primarily responsible mechanisms.[15] However, the underlying causes and clinical significance are still debated.

In recent meta-analyses, elevated troponin rates among all adult AIS patients vary between 9.7% and 54.4%.[16] This rate was 18.5% in our study. The literature has conflicting results for the correlation of NIHSS and troponin. In a prospective observational study conducted by Ahn et al., 1,092 IS patients were observed, and the NIHSS median score was 8 (IQR: 25–75; 3–14) in patients with increased troponin levels; the median score was 4 (IQR: 25–75; 2–8) in patients with minimally increased troponin levels, and the median score was 3 (IQR: 25–75; 1–6) in patients with undetectable troponin levels.[17] However, in Abdi et al.'s study, no significant difference was found between the troponin levels of patients with NIHSS scores of 0–9 and patients with scores between 10–42 (p=0.140).[12] We believe that the lack of a significant correlation between NIHSS and troponin in our study may be related to the fact that the center where we conducted the research was not a stroke center; therefore, most of our cases consisted of patients with mild symptoms who could be admitted as outpatients.

In addition to predicting the severity of AIS, studies evaluating the predictive power of troponin on long-term neurological outcomes exist. In one of these, 81 (79.4%) of 103 patients with troponin elevation were found to have mRS >2 at the time of hospital discharge.[18] In the same study, a major neurological improvement, defined as an improvement in an NIHSS score of ≥8 points or regression of NIHSS between 0–1, was detected in 26.4% of patients with elevated troponin levels and 51.5% of patients with normal troponin levels.[18] Similar to the literature, mRS levels showed a significant difference between the troponin-positive and negative groups in our study (p=0.002). Mild stroke patients made up the majority of all patients. Despite this, this observed difference can be interpreted as troponin being a good marker for an IS outcome.

In studies examining the predictive role of troponin in terms of mortality in IS, the relative risk of increased troponin in all-cause deaths was found to be

2.53 (95% CI; 2.09–5.98).[3] In Esteak et al.'s study, patients with high troponin levels had a higher 90-day mortality (p=0.022).[4] In our study, although patients were categorized only according to the reference range and no classification such as normal-mild elevation-severe elevation was made, the findings were consistent with the literature.

Elevated troponin in AIS may be due to 2 different reasons. These are primary changes resulting from pre-existing cardiac problems and secondary findings superimposed on primary changes before and after the stroke.[17-20] In our study, heart failure was more common in the troponin-positive group. These results may be from a two-way relationship between the heart and brain, and the pathologies of both organs may be predisposing for the other.

In the present study, urea and creatinine levels were significantly higher in the group with high troponin. In the beginning, we excluded patients with chronic renal failure and excluded troponin elevations that may have been due to this condition. However, acute deterioration in renal functions may be the result of the pathophysiological process of stroke and could be an indicator of a poor prognosis. Abdi et al. found that IS patients with increased troponin levels also had higher creatinine levels and showed that higher creatinine levels were correlated with stroke severity.[12] Our study demonstrated that troponin plays a crucial prognostic role in AIS. However, clarifying the underlying pathogenesis with future studies is necessary.

The study's most important limitation is that it was conducted in a hospital that does not serve as a stroke center. For this reason, many patients were referred to an external center, and the treatments given could not be examined in detail. Therefore, the treatments applied may have played a role in prognosis. Additionally, most of our patients were in the mild stroke group. Another limitation is that patients with atrial fibrillation were excluded. At the beginning of the study, it was decided to exclude patients with atrial fibrillation so that patients with arrhythmia would not have a distracting effect regarding troponin positivity. However, because we excluded a critical risk factor for stroke, this may have caused us to exclude a significant group of patients. Another limitation is we included the patients with heart failure. Despite there was a significant difference between in group comparison of HF frequency in troponin positive and negative groups, nine HF patients had distributed to groups, nearly equal (4 patient in the troponin negative group and 5 in the positive group). We think that troponin positivity might be related to stroke-heart syndrome; but we couldn't exclude the heart failure itself as a reason for this positivity.

In conclusion, troponin may be an important prognostic factor for mortality and poor neurological outcomes, even in patients experiencing mild strokes. In our study, no significant correlation was found between NIHSS and troponin on admission, and this might be due to the mild stroke severity of most of our patients. As a result, troponin levels measured during ED admission can be used as a biomarker to determine the prognosis in patients presenting with AIS.

Ethics Committee Approval: Our study was approved by the Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 08.03.2022, decision no: 2012-KAEK-15/2489).

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

Author Contributions: Concept – GCI, OK, YC; Supervision – GCI, SKC, YC; Materials – SY, OK; Data Collection and/or Processing – SY, GCI, FK, OK; Analysis and/or Interpretation – SY, GCI, FK, SKC, OK, YC; Writing – SY, GCI, FK

Peer-review: Externally peer-reviewed.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):216-223 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):216-223*

The Effect of Disease Management Education Provided to Women with Rheumatoid Arthritis on Quality of Life, Anxiety, and Depression: A Randomized Controlled Study

Romatoid Artritli Kadınlara Verilen Hastalık Yönetimi Eğitiminin Yaşam Kalitesi, Anksiyete ve Depresyon Üzerine Etkisi: Randomize Kontrollü Bir Çalışma

[1]Irem YILDIZ CILENGIROGLU, [1]Serap ÜNSAR

[1]Trakya University, Faculty of Health Sciences, Department of Internal Medicine Nursing, Balkan Campus, Edirne, Türkiye

Irem Yildiz Cilengiroglu: https://orcid.org/0000-0001-8276-0158
Serap Unsar: https://orcid.org/0000-0001-7723-8816

ABSTRACT

Objective: The aim of this randomized controlled trial is to investigate the effect of education of disease management on quality of life, anxiety and depression in women with rheumatoid arthritis.

Materials and Methods: The study included 66 women with rheumatoid arthritis at a university hospital in Türkiye. Data were obtained via "Rheumatoid Arthritis Quality of Life Scale", "Health Assessment Questionnaire", and "Hospital Anxiety Depression Scale".

Results: A significant difference was found between the intervention group's mean scores on the "Rheumatoid Arthritis Quality of Life Scale" at baseline and third month ($p < 0.05$). Significant correlations were found between the intervention group's Rheumatoid Arthritis Quality of Life Scale scores and the sociodemographic and disease-related characteristics such as education level and having arthritis-related deformities ($p < 0.05$).

Conclusions: The findings obtained in this study showed that education is an effective method to increase the quality of life of women with rheumatoid arthritis. Individual disease management training provided by rheumatology nurses to women with Rheumatoid Arthritis is considered to improve quality of life. Therefore, women with rheumatoid arthritis are recommended to receive psychosocial support in managing their disease and symptoms.

Keywords: Anxiety, depression, quality of life, rheumatoid arthritis, women

ÖZ

Amaç: Bu randomize kontrollü araştırma, Romatoid Artritli kadınlara hastalık yönetimine ilişkin verilen eğitimin yaşam kalitesi, anksiyete ve depresyon üzerine etkilerini belirlemek amacıyla planlandı.

Materyal ve Metot: Araştırma, Romatoid Artritli 66 kadın hasta (32 deney, 34 kontrol) ile bir üniversite hastanesinin Romatoloji kliniği ve polikliniğinde yürütüldü. Veriler; "Romatoid Artrit Yaşam Kalitesi Ölçeği", "Sağlık Değerlendirme Anketi" ve "Hastane Anksiyete Depresyon Ölçeği" kullanılarak toplandı.

Bulgular: Deney grubundaki hastaların "Romatoid Artrit Yaşam Kalitesi Ölçeği" başlangıç ve üçüncü ay puan ortalamaları arasında anlamlı fark bulundu ($p < 0,05$). Deney grubunun Romatoid Artrit Yaşam Kalitesi Ölçeği puanları ile eğitim düzeyi ve artrit nedeniyle etkilenen deformitesi olma durumu gibi sosyodemografik ve hastalığa ilişkin özellikleri arasında anlamlı ilişkiler bulundu ($p < 0,05$).

Sonuç: Bu çalışma, hastalık yönetimine ilişkin verilen eğitimin Romatoid Artritli kadınların yaşam kalitesi üzerindeki etkisini göstermektedir. Romatoloji hemşireleri tarafından Romatoid Artritli kadınlara hastalık yönetimine ilişkin verilecek bireysel eğitimin yaşam kalitesini arttıracağı düşünülmektedir. Romatoid Artritli kadınlara semptomlara bağlı yaşadıkları sorunlara yönelik psikososyal destek almaları önerilmektedir.

Anahtar Kelimeler: Anksiyete, depresyon, kadın, romatoid artrit, yaşam kalitesi

Sorumlu Yazar / Corresponding Author:
Irem Yildiz Cilengiroglu
Trakya University, Faculty of Health Sciences, Department of Internal Medicine Nursing, Balkan Campus, Edirne, Türkiye
Tel: +905385260034
E-mail: iremyildiz@trakya.edu.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 02/02/2024
Kabul Tarihi/ Accepted: 04/07/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Yıldız Çilengiroğlu İ and Ünsar S. The Effect of Disease Management Education Provided to Women with Rheumatoid Arthritis on Quality of Life, Anxiety, and Depression: A Randomized Controlled Study. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):216-223. doi: 10.26453/otjhs.1430540

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that primarily affects the synovial joints. Inflammation of joints damages the cartilage and causes the joints to erode.[1,2] The prevalence of RA is three times higher in women than in men.[3] In Türkiye, the prevalence of RA has been reported to be 0.56%, and 0.89% in women.[4]

Rheumatoid arthritis, which is characterized by recurrent cycles of exacerbation and remission, causes disability and decreases the functional status of the patients.[5] Patients who are unable to perform daily activities due to pain and joint involvement caused by synovial inflammation have limited mobility.[6] Disease symptoms can lead to a reduction in quality of life due to pain, fatigue, and disability, which can cause mood changes such as anxiety and depression.[3,7] Depression is highly prevalent in patients with RA, with some studies reporting rates as high as 41.5%, surpassing the general population.[8] In a study, the prevalence of depression and anxiety in patients with RA was found to be 23.3% and 42.3%, respectively.[9]

Patient education is important for the management of RA and the reduction of symptoms as it contributes to the patient's adaptation to the treatment and the maintenance of a healthy lifestyle.[10] Previous studies have reported that patients with RA in the intervention group have a higher quality of life after training. Education on individual disease management has been shown to increase the quality of life.[7,11] When the patient is educated in disease management, the effectiveness of the treatment increases, functional competence is provided, and the quality of life can be increased. Moreover, healthcare professionals play an important role in disease management, especially rheumatology nurses, who spend more time with patients. Nurses should support individuals to improve their daily lives, adapt to illness, and improve their quality of life.[11,12]

This study aimed to examine the effect of training provided by nurses who interact with patients the most on their quality of life, anxiety and depression. There are many similar studies in the international arena, but when looked at nationally, it was the first time in our country. Therefore, our study purposed to examine the effect of education on disease management, on the quality of life, anxiety and depression of women with RA.

MATERIALS AND METHODS

Ethical Considerations: A University Research Ethics Committee confirmed the study protocol, which adhered to the Helsinki Declaration (Date: 17.09.2018 Decision no: 16/23). The patients were briefed about the study before it began, and both written and verbal consent was received.

Study Design: This prospective pretest and posttest study was carried out as a randomized controlled trial between February 2019 and October 2019 at the outpatient clinic of the Department of Rheumatology in a university hospital in Türkiye. The trial was registered in ClinicalTrials.gov (Protocol ID-NCT04850183).

Study Participants: Women with rheumatoid arthritis who met the 2010 American College of Rheumatology (ACR) criteria, had a disease duration of at least 6 months and were 18 years of age or older voluntarily agreed to participate in this study.[13]

When the literature was examined, there was no study similar to our study done in Türkiye. This study aimed to reach a medium effect, therefore performed with effect size d=0.60, 80% (1 – β error) power, and 95% (α error) confidence level. The sample size required a total of 72 patients, 36 patients for each group (G* Power 3.1.9.4). Anticipating a possible sample loss, we increased the sample size by 10%. Therefore, 40 patients were included in each group, thus the total number of patients enrolled was 80.

Randomization: A single-blind technique was used to eliminate any bias. The patients were selected using a simple random sampling method and divided into intervention and control groups using the Research Randomizer program. Consolidated Trial Standards of Reporting List (CONSORT) principles were the foundation for the study's design and conduct (Figure 1).

Study Instruments: The Patient Information Form, Rheumatoid Arthritis Quality of Life Scale, the Health Assessment Questionnaire, and the Hospital Anxiety Depression Scale were used to collect data.

Patient Information Form: The form was developed by researchers in line with a literature.[7,10,11]The form consisted of eight questions about sociodemographic characteristics (age, marital status, education, etc.), clinical diagnosis, medication of RA, concomitant chronic disease, and deformity in consequence of arthritis.

Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL): The questionnaire consists of 30 questions. The scores ranged from 0 to 30, with high scores showing poor quality of life. In 2003, Kutlay et al. verified the scale's validity and reliability.[14]

Stanford Health Assessment Questionnaire (HAQ): The HAQ is a functional status questionnaire whose score has been demonstrated to correspond with disease activity indicators. The HAQ is composed of 20 questions that are divided into eight categories: waking up, moving, feeding, dressing and grooming, hygiene, grip, reach, and tasks. The score is computed as an average of eight domains with scores vary-

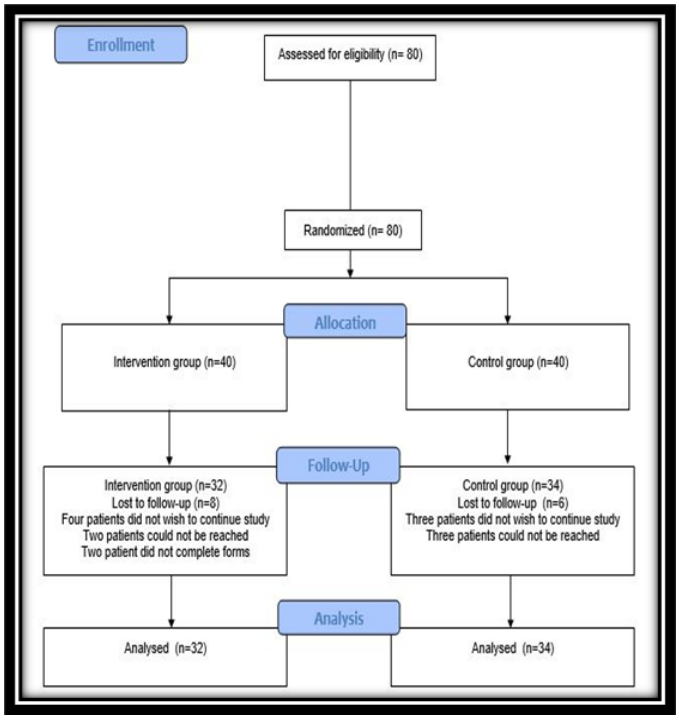

Figure 1. CONSORT 2010 Flow Diagram.

ing from 0 to 3, with a higher score displaying significant impairment. Kucukdeveci et al. verified the scale's validity and reliability in 2004.[15]

Hospital Anxiety and Depression Scale (HADS): The HADS includes both anxiety and depression sub-scales and consists of 14 items, 7 of which examine depression (Hospital Anxiety and Depression Scale-Depression, HAD-D) and 7 of which examine anxiety (Hospital Anxiety and Depression Scale-Anxiety, HAD-A). Patients with scores above these scores are regarded as a risk category. The purpose of the scale is not to diagnose but to assess the risk group by checking for anxiety and depression over a short period. Aydemir et al. verified its validity and reliability in 1997.[16]

Data Collection: Data were collected through face-to-face interviews. The researcher collected data in accordance with the randomization table.

Standard Intervention: Patients are informed about medication and its side effects by rheumatology specialists at the time of diagnosis. Regular education is not provided to patients. If patients had a question or medical problem, they could get information if they had made an appointment and came for a visit. Nurses are the health professionals who interact the most with patients. For this reason, it is an important responsibility of nurses to support and inform patients with such a complicated disease. It is crucial for them to not only oversee the treatment but also to manage the physical, mental, cognitive, and spiritual complications of the disease. In this context, an educational booklet was created that nurses can use in informing patients with RA in addition to standard care.

This study was conducted in three stages.

First Stage: Rheumatoid Arthritis Patient Education Booklet: Researchers prepared the booklet's content in accordance with the literature.[7,9,17] The education topics included description, symptoms, and signs of RA, diagnostic methods, treatment choices, information on medications, RA in pregnancy, disease management, nutritional recommendations, emotional health, and support in daily living. After taking expert opinions, the booklet was revised according to the recommendations.

Second Stage: Before the study, patients in all groups were informed about the study. Baseline data were obtained from both intervention and control groups using the study instruments. All the data collection tools were completed by the patient's self-reports. While the patients in the control group received standard care, patients in the intervention group were informed by the researcher via an education booklet. The education took an average of 30 minutes. The training was done individually. It was done when they came to the outpatient clinic for routine controls. After the training was over, the questions of the patients in the intervention group were answered.

Third Stage: Third months after the baseline, the patients in all groups underwent a routine examination, whereby the study instruments were applied to the patients a second time.

Data Analysis: Data were analyzed using the IBM SPSS 20.0 program. Socio-demographic data were analyzed using the mean, standard deviation, and frequency. Mann-Whitney U tests were used to compare variables in two groups. Pearson Chi-Square Test, Continuity Correction test and Fisher's Exact test were used to compare qualitative data. The Wilcoxon signed-rank test was used for the paired comparisons in the comparison of qualitative data. The significance level was set at $p \leq 0.05$.

RESULTS

Table 1 shows the sociodemographic and disease-related characteristics of the women. When the personal and disease-related characteristics in the intervention and control groups were examined, they were found to be similar in terms of age, educational and marital status, period of clinical diagnosis, treatment of RA, chronic diseases, and deformities affected by arthritis. The patients' characteristics showed a homogeneous distribution between the groups.

The mean RAQoL score of the women in the intervention group was lower in the 3rd month (p=0.004) compared to the baseline. There was no significant difference between the HAQ and HADS mean scores of the women after training (p >0.05). There was no significant difference found between the RAQoL, HAQ, and HADS mean scores of women in the control group in the 3rd month (p >0.05). However, the intervention group had a higher mean HAD-D score at baseline. Additionally, in the 3rd month, the mean HAD-D score was higher in the intervention group compared to the control group (p=0.038) (Table 2).

Table 1. The sociodemographic and disease-related characteristics of the patients.

Characteristics		Intervention group (n=32)	Control group (n=34)	Test and p values
Age	Min-Max	30-73	39-82	Z: 489.0
	Mean±SD	56.46±11.88	59.50±9.97	p*: 0.480
Time of clinical diagnosis (year)	Min-Max	1-55	1-56	Z: 410.0
	Mean±SD	18.59±12.68	13.55±10.66	p*: 0.085
Education Status; n (%)	Primary and below (≤5 years)	21 (65.6)	20 (58.8)	χ^2:0.324
	Secondary and above (≥6 years)	11 (34.4)	14 (41.2)	p†: 0.569
Marital Status; n (%)	Married	28 (87.5)	31 (91.2)	χ^2:0.007
	Single	4 (12.5)	3 (8.8)	p‡: 0.932
Treatment of Rheumatoid Arthritis; n (%)	cDMARDs	9 (28.1)	9 (26.5)	χ^2:0.190
	bDMARDs	7 (21.9)	9 (26.5)	p†: 0.910
	cDMARD+bDMARD	16 (50.0)	16 (47.1)	
Chronic disease; n (%)	No	15 (46.9)	13 (38.2)	χ^2:0.504
	Yes	17 (53.1)	21 (61.8)	p†: 0.478
Deformity-inconsequence by arthritis; n (%)	No	11 (34.4)	7 (20.6)	χ^2:1.580
	Yes	21 (65.6)	27 (79.4)	p†: 0.209

*: Mann Whitney U Test; †: Pearson Ki-kare Test; ‡: Continuity Correction Test; §: Fisher's Exact Test, Min: Minimum, Max: Maximum, Mean±SD: Mean ±Standart deviation; bDMARD: biologic disease-modifying antirheumatic drugs cDMARD: conventional disease-modifying antirheumatic drugs.

Table 2. The distribution of RAQoL, HAQ, and HADS mean scores of the groups according to the months which baseline and third month.

Scales		Intervention group (n=32)	Control group (n=34)	Test value	p*
		Mean±SD	Mean±SD		
RAQoL	Baseline	19.50±7.29	14.97±8.80	377.00	**0.032**
	3rd month	17.31±6.49	15.38±8.36	455.00	0.253
Test value		-2.876	-0.918		
p†		**0.004**	0.358		
HAQ	Baseline	0.46±0.42	0.40±0.37	495.50	0.532
	3rd month	0.45±0.43	0.40±0.35	505.00	0.616
Test value		-0.086	-0.178		
p†		0.932	0.858		
HAD-A	Baseline	10.06±5.41	8.79±5.04	482.50	0.429
	3rd month	10.46±5.19	8.73±5.01	438.50	0.175

RAQoL: Rheumatoid Arthritis Quality of Life Questionnaire; **HAQ:** Stanford Health Assessment Questionnaire; **HAD-A:** Hospital Anxiety and Depression Scale-Anxiety; **HAD-D:** Hospital Anxiety and Depression Scale-Depression; *: Mann Whitney U test; †: Wilcoxon Signed Ranks test; Mean±SD: Mean±Standart deviation.

Table 2. Continue.

Test value		-0.669	-0.213		
p†		0.504	0.832		
HAD-D	Baseline	8.21±4.74	6.52±3.74	422.00	0.116
	3rd month	8.71±4.61	6.67±3.68	383.00	**0.038**
Test value		-1.463	-0.544		
p†		0.144	0.586		

RAQoL: Rheumatoid Arthritis Quality of Life Questionnaire; **HAQ:** Stanford Health Assessment Questionnaire; **HAD-A:** Hospital Anxiety and Depression Scale-Anxiety; **HAD-D:** Hospital Anxiety and Depression Scale-Depression; *: Mann Whitney U test; †: Wilcoxon Signed Ranks test; Mean±SD: Mean±Standart deviation.

The mean RAQoL scores of the patients in the intervention group declined significantly in the 3rd month, regardless of their education level (p=0.050 for primary school and below; p=0.029 for secondary school and above). The quality of life of women, regardless of their education levels, in the intervention group improved after training than the control group. There was no significant difference in the HAQ mean scores of women with RA after training (p >0.05) (Table 3).

In the intervention group, RAQoL mean scores of women with deformities affected by arthritis were significantly lower than those control group after training (p =0.008). After training, women with deformities affected by arthritis in the intervention group had a higher quality of life than the control group in 3rd month. There was no significant difference between the mean HAQ and HADS scores in the intervention group after training (p > 0.05) (Table 4).

Table 3. Comparison of the scales (RAQoL, HAQ, HAD-A, HAD-D) mean scores of the groups according to educational status.

Scales		**Educational Status**					
		Primary and below			**Secondary and above**		
		Intervention group (n=21) Mean±SD	Control group (n=20) Mean±SD	p*	Intervention group (n=11) Mean±SD	Control group (n=14) Mean±SD	p*
RAQoL	Baseline	21.33±6.94	15.80±8.72	**0.045**	16.00±6.91	13.78±9.10	0.443
	3rd month	19.42±5.58	16.75±7.63	0.205	13.27±6.42	13.42±9.23	0.742
p†		**0.050**	0.183		**0.029**	0.888	
HAQ	Baseline	0.53±0.41	0.49±0.36	0.804	0.32±0.42	0.28±0.35	0.486
	3rd month	0.54±0.42	0.49±0.34	0.875	0.30±0.42	0.26±0.34	0.435
p†		0.598	0.532		0.180	0.340	
HAD-A	Baseline	10.76±5.29	9.00±5.56	0.289	8.72±5.64	8.50±4.40	0.912
	3rd month	11.23±4.80	9.10±5.47	0.174	9.00±5.83	8.21±4.42	0.762
p†		0.668	0.715		0.257	0.414	
HAD-D	Baseline	9.19±4.43	7.05±4.14	0.094	6.36±4.96	5.78±3.06	0.978
	3rd month	9.90±4.03	7.40±3.95	**0.031**	6.45±4.98	5.64±3.10	0.912
p†		0.177	0.277		0.655	0.458	

RAQoL: Rheumatoid Arthritis Quality of Life Questionnaire; **HAQ:** Stanford Health Assessment Questionnaire; **HAD-A:** Hospital Anxiety and Depression Scale-Anxiety; **HAD-D:** Hospital Anxiety and Depression Scale-Depression; *: Mann Whitney U Testi; †: Wilcoxon Signed Ranks Test; Mean±SD: Mean±Standart deviation.

Table 4. Comparison of the mean scores for the scales (RAQoL, HAQ, HAD-A, HAD-D) among the groups based on arthritis-related deformities.

Scales		**Deformities resulting from arthritis**					
		Yes			**No**		
		Intervention group (n=21) Mean±SD	Control group (n=27) Mean±SD	p*	Intervention group (n=11) Mean±SD	Control group (n=7) Mean±SD	p*
RAQoL	Baseline	19.80±7.83	15.59±8.73	0.098	18.90±6.42	12.57±9.34	0.134
	3rd month	17.04±6.82	15.77±8.19	0.539	17.81±6.11	13.85±9.49	0.296
p†		**0.008**	0.690		0.229	0.109	
HAQ	Baseline	0.47±0.42	0.41±0.36	0.603	0.44±0.42	0.36±0.40	0.553
	3rd month	0.47±0.46	0.40±0.35	0.602	0.42±0.37	0.38±0.38	0.785

RAQoL: Rheumatoid Arthritis Quality of Life Questionnaire; **HAQ:** Stanford Health Assessment Questionnaire; **HAD-A:** Hospital Anxiety and Depression Scale-Anxiety; **HAD-D:** Hospital Anxiety and Depression Scale-Depression; *: Mann Whitney U Testi; †: Wilcoxon Signed Ranks Test; Mean±SD: Mean±Standart deviation

Table 4. Continue.

p†		0.892	0.636		0.918	0.109	
HAD-A	Baseline	9.14±5.86	9.18±4.97	0.661	11.81±4.09	7.28±5.43	0.050
	3rd month	9.66±5.73	9.22±4.80	1.000	12.00±3.76	6.85±5.75	0.050
p†		0.501	0.811		0.865	0.317	
HAD-D	Baseline	7.76±4.99	6.88±3.88	0.545	9.09±4.30	5.14±2.96	0.056
	3rd month	8.23±5.15	7.11±3.75	0.364	9.63±3.38	5.00±3.05	**0.018**
p†		0.275	0.499		0.348	0.317	

RAQoL: Rheumatoid Arthritis Quality of Life Questionnaire; **HAQ:** Stanford Health Assessment Questionnaire; **HAD-A:** Hospital Anxiety and Depression Scale-Anxiety; **HAD-D:** Hospital Anxiety and Depression Scale-Depression; *: Mann Whitney U Testi; †: Wilcoxon Signed Ranks Test; Mean±SD: Mean±Standart deviation

DISCUSSION AND CONCLUSION

The present study determined that the life quality of women with RA improved after training. It can be said that the education given to patients with RA positively affects their quality of life.

In this study, we found that women with RA, regardless of their education level, improved their quality of life after training. Initially, the depression levels of women in the intervention group were higher than those in the control group. Therefore, after the training, the depression levels of the patients in the intervention group were found to be slightly higher than those in the control group. Al-Jabi et al. found that a higher level of education was associated with an improved quality of life in RA patients.[18] In patients with RA, Zhang et al. found that low quality of life and low level of education were risk factors for depression and anxiety.[19] The current study results suggest that women's willingness to learn and educate themselves had a positive impact on their quality of life.

In our study, the quality of life of women with deformities that occurred as a consequence of arthritis was higher after training. In a previous study conducted in patients with RA, the number of swollen joints was found to be associated with depression, with a high number of sensitive joints indicating poor quality of life.[9] In a recent study, it is stated that the quality of life of patients with RA is significantly affected negatively by having a joint deformity.[20] We think that the majority of women with RA who had arthritis-related deformities and taking conventional and biologic DMARDs together are willing to education, and women with RA in this group attribute more importance to education for symptom management, and this improves their quality of life.

In our study, no change was observed in the functional status of women with RA in the intervention and control groups in daily life at the baseline and 3rd month. Gronning et al. stated that there was no change in the functional status of the patients in the intervention group before and after the training.[21] In a study by Abourazzak et al. evaluating the long-term effects of training, no change was found in the patients' functional status in daily life at the beginning and 3 years later.[22] There is a need for more evidence-based research evaluating the functional status in the daily life of individuals with rheumatoid arthritis.

In conclusion, our study determined that the quality of life of women with RA improved after training. We suggest that women with RA should be trained in disease management by rheumatology nurses at regular intervals using educational material. Considering sociodemographic (marital status, education, etc.) and disease-related characteristics (treatment of RA, deformity, chronic disease, etc.) are essential in training programs planned for women with RA. The study has some limitations. A small sample is one of them. Additionally, the study was conducted in a single center in Türkiye, and the effectiveness of the training was only evaluated three months later. Future studies should investigate the long-term effects of patient training. The prevalence of RA is three times higher in women than in men.[3] In Türkiye, the prevalence of RA in women was reported to be 0.89%.[4] The significance of the study, therefore, lies in the fact that it was a randomized, controlled study conducted on women.

Ethics Committee Approval: Our study was approved by the Trakya University Ethics Committee (Date: 17.09.2018, decision no: 16/23). The study was carried out following the Helsinki Declaration.

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

Author Contributions: Concept - IYC, SU; Supervision – SU, IYC Materials – IYC; Data collection and/or Processing – IYC; Analysis and/or Interpretation - IYC, SU; Writing - IYC

Peer-review: Externally peer-reviewed.

Funding Information: This study was supported by Trakya University Scientific Research Project Unit. Project number: TUBAP 2019/02

Acknowledgements: We want to thank the head of the rheumatology department, Prof. Dr. Hakan Emmungil, Assoc. Dr. Barış Yılmazer, rheumatology nurses and the patients with rheumatoid arthritis for

their contributions.

Other Information: This study was presented as an oral presentation at the 2nd International Internal Medicine Nursing Congress (17-19 December 2020).

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):224-231 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):224-231*

Evaluation of Cold Conization Indications and Results

Soğuk Konizasyon Endikasyonlarının ve Sonuçlarının Değerlendirilmesi

[1]Sinem TEKİN

[1]Department of Obstetrics and Gynecology, Haseki Training and Research Hospital, Istanbul; Türkiye

Sinem Tekin: https://orcid.org/0000-0003-4183-6472

ABSTRACT

Objective: The aim of this study was to determine the efficiency and indications of cold knife conization in the treatment of high-grade cervical lesions.

Materials and Methods: This study included patients with high-grade cervical lesions treated with cold knife conization (CKC) within 9 years. Histopathological correlation analyses were carried out among the smear, colposcopic biopsy (CBx), CKC results, and total hysterectomy specimens available.

Results: One hundred thirty-one cold knife cone biopsy cases were analyzed for this study. The most common pathology was cervical intraepithelial neoplasia (CIN) II–III, with a frequency of 64 (48.9%). Other conization results in order of frequency were as follows: CIN I at a rate of 29 (22.1%), Carcinoma (Ca) at 19 (14.5%), cervicitis at 14 (10.7%), and negative results at 5 (3.8%).

Conclusions: CKC remains an acceptable option in the treatment of CIN and microinvasive carcinoma of the cervix, and the excellent diagnostic and therapeutic efficacy of CKC is well-known and confirmed. When properly performed, the procedure has a low risk of complications and provides an accurate histological representation of the disease process. It is also curative in most cases. Of course, excellent clinical results still require careful, long-term, and attentive follow-up.

Keywords: Cervical intraepithelial neoplasia, cervical smear, cold knife conization

ÖZ

Amaç: Bu çalışmanın amacı yüksek dereceli servikal lezyonların tedavisinde soğuk konizasyonunun etkinliğini ve endikasyonlarını belirlemektir.

Materyal ve Metot: Bu çalışmaya 9 yıllık süreçte yüksek dereceli servikal lezyonu olan ve soğuk konizasyon ile tedavi edilen hastalar dahil edildi. Smear, kolposkopik biyopsi, soğuk konizasyon sonuçları ve mevcut total histerektomi spesimenleri arasında histopatolojik korelasyon yapıldı.

Bulgular: Yüz otuz bir soğuk koni biyopsisi bu çalışma için analiz edildi. En sık görülen patoloji 64 (%48,9) ile CIN II-III idi. Diğer konizasyon sonuçları sıklık sırasına göre şöyledir; CIN I 29 (%22,1), Karsinom (Ca) 19 (% 14,5) , servisit 14 (%10,7), negatif 5 (%3,8).

Sonuç: Soğuk konizasyon, serviksin servikal intraepitelyal neoplazi (CIN) ve mikroinvaziv karsinomunun tedavisinde kabul edilebilir bir seçenek olmaya devam etmekte ayrıca tanısal ve terapötik etkinliği iyi bilinmektedir. Uygun şekilde yapıldığında, doğru bir histopatolojik tanı sağlar ve düşük komplikasyon riskine sahiptir; ayrıca çoğu vakada küratiftir. Elbette, mükemmel klinik sonuçlar yine de dikkatli, uzun süreli ve özenli bir takip gerektirmektedir.

Anahtar Kelimeler: Servikal intraepitelyal neoplazi, servikal smear, soğuk konizasyon

Sorumlu Yazar / Corresponding Author:
Sinem Tekin
Department of Obstetrics and Gynecology, Haseki Training and Research Hospital, Sultangazi, İstanbul, Türkiye.
Tel: +905057900571
E-mail: drsinemtekin@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 27/02/2024
Kabul Tarihi/ Accepted: 27/07/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Tekin S. Evaluation of Cold Conization Indications and Results. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):224-231. doi: 10.26453/otjhs.1443698

INTRODUCTION

Cervical health is recognized as a critical component of the female reproductive system, playing an important role in fertility and overall well-being. However, in certain cases, abnormal changes can occur in the cells of the cervix, a condition known as cervical intraepithelial neoplasia (CIN). CIN refers to precancerous changes in the epithelial cells of the cervix and is a significant health risk for women worldwide, potentially progressing to cervical cancer if left untreated.[1] CIN cases are histologically confirmed on a biopsy specimen and categorized as CIN I (mild dysplasia), CIN II (moderate dysplasia), or CIN III (severe dysplasia or carcinoma in situ). CIN II and CIN III patients must be treated since untreated cases have low spontaneous regression rates (32-43%) and a high risk of invasive cancer (5-22%).[2]

Surgical techniques are available for the treatment of high-grade CIN. Cold knife cervical conization (CKC), a conservative surgical approach for treating CIN II and CIN III, was first described by Lisfranc in 1815 and can be performed using a cold knife, CO2 laser, or electrical loop electrodes (LLETZ, i.e., loop electrosurgical excisional procedure, LEEP).[3]

In CKC surgery, a cone-shaped piece of the cervix is excised to remove a cervical lesion and the entire transformation zone.[4] CKC allows the histological confirmation of the lesion, the exclusion of invasive neoplasia, and the evaluation of resection margins. CKC provides more extensive tissue sampling for pathology than other procedures, but a wide and deep cervical cone excision can cause bleeding, infection, cervical stenosis, and mid-trimester pregnancy loss.[5] The rate of success (i.e., no residual disease at follow-up) of knife cone biopsy was reported to be 90% to 94% in non-randomized studies.[6]

We aimed to evaluate the indications and histopathological outcomes of Turkish women undergoing CKC for the treatment of CIN II/III.

MATERIALS AND METHODS

Ethic Committee Approval: The Declaration of Helsinki was followed in the study. Our study was approved by the Non-Interventional Clinical Research Ethics Committee of Kartal Training and Research Hospital (Date:30.05.2017, decision no: 2017/514/108/7).

Data collection: Patient identification in Kartal Training and Research Hospital was accomplished by examining admission logs from accessible medical data. The data were obtained from the hospital information system by experienced research physicians.

Study Design and Participants: This retrospective study conducted at Kartal Training and Research Hospital's Department of Obstetrics and Gynecology between 2008 and 2017 involved 131 patients who underwent CKC for diagnosed CIN II and CIN III based on cervical cytology or biopsy. Other indications for CKC included unsatisfactory colposcopy, positive endocervical curettage, and suspicion of microinvasive disease, while women with a history of hysterectomy, recent pregnancy, or other gynecologic malignancies were excluded from the study. Patients undergoing CKC underwent scalpel excisions under general or regional anesthesia. Colposcopic examination with 3% to 5% acetic acid to delineate the transformation zone, followed by a circumferential incision, was made with a long-handled scalpel. Starting posteriorly, the scalpel blade was placed at the desired depth and direction, and a conical portion of the cervix was then removed. Hemostasis was achieved using bilateral interrupted vertical sutures, and vaginal packing was inserted for 12 hours. Specimens were evaluated by experienced pathologists at our hospital's Pathology Department. Positive margins were defined by the presence of HSIL or cancer within ≤1 mm of the resection surface. Further surgery, including radical hysterectomy and pelvic lymphadenectomy, was performed for patients with cancerous margins or cases unsuitable for fertility preservation. For each patient, data were collected on age, preoperative cytology and colposcopy results, indication for conization, histology of cone specimen, and results of subsequent follow-up and management.

Statistical Analysis: The statistical analyses were performed using SPSS version 23.0 (IBM SPSS, USA) or GraphPad Prism 9.x (GraphPad, USA). Continuous variables were represented as mean (M) ±standard deviation (SD); discrete variables were represented as frequency (n) and percentage distribution.

RESULTS

131 CKC cases were analyzed in this study. First pap test results (FPRs) were available for 125 of these patients. Figure 1A shows the FPR of 125 cases assessed, and the results of 98 colposcopic biopsies (CBx) were available (Figure 1B). Figure 1C shows the distribution of pathologies in endocervical curettage (ECC) specimens of 105 cases and Figure 1D shows the results of 31 patients who underwent LEEP prior to conization. Conization findings for 131 patients are shown in Figure 1E. The most common pathology was CIN II-III with a frequency of 64 (48.9%). The highest mean age was 59.6±13.60 years in the carcinoma (Ca)/carcinoma in situ (CIS) group. Hysterectomy was performed on 45 patients, with pathology outcomes depicted in Figure 1F. Ca emerged as the predominant pathology among hys-

terectomized women, accounting for 14 (31.1%). The depth of invasion was measured in 10 hysterectomized patients with Ca pathology: 3 mm in 2 patients, 8 mm in 2 patients, 9 mm in 1 patient, 10 mm in 2 patients, 12 mm in 1 patient, and 13 mm in 2 patients. The mean depth was 8.9 ± 3.60 mm. Furthermore, radiotherapy was administered to 9 patients with Ca pathology identified post-hysterectomy. Patients who underwent CKC or subsequent hysterectomy were followed up with smear tests at 3, 6, and 9 months, coded as the first follow-up pap tests (FPTs), as shown in Figure 1G. One patient who had a type 2 hysterectomy for squamous cell carcinoma had a 6-month follow-up smear showing carcinoma. The 2nd FPTs were performed for 1 year (Figure 1H). Among the 99 patients with 2nd FPTs, 92 (92.9%) had normal results. 2 (2%) patients had ASC-US, 2 (2%) patients had CIN I, 2 (2%) patients had CIN II-III, and 1 (1%) patient had VAIN II. The 3rd FPTs were performed between years 1 and 8. Most of the samples were taken in years 3 and 4. The results of the 3rd FPTs of 67 cases are shown in Figure 1I. 64 (95.5%) of these results were normal, 1 (1.5%) result was compatible with CIN I, 1 (1.5%) was compatible with VAIN II, and 1 (1.5%) was compatible with Ca.

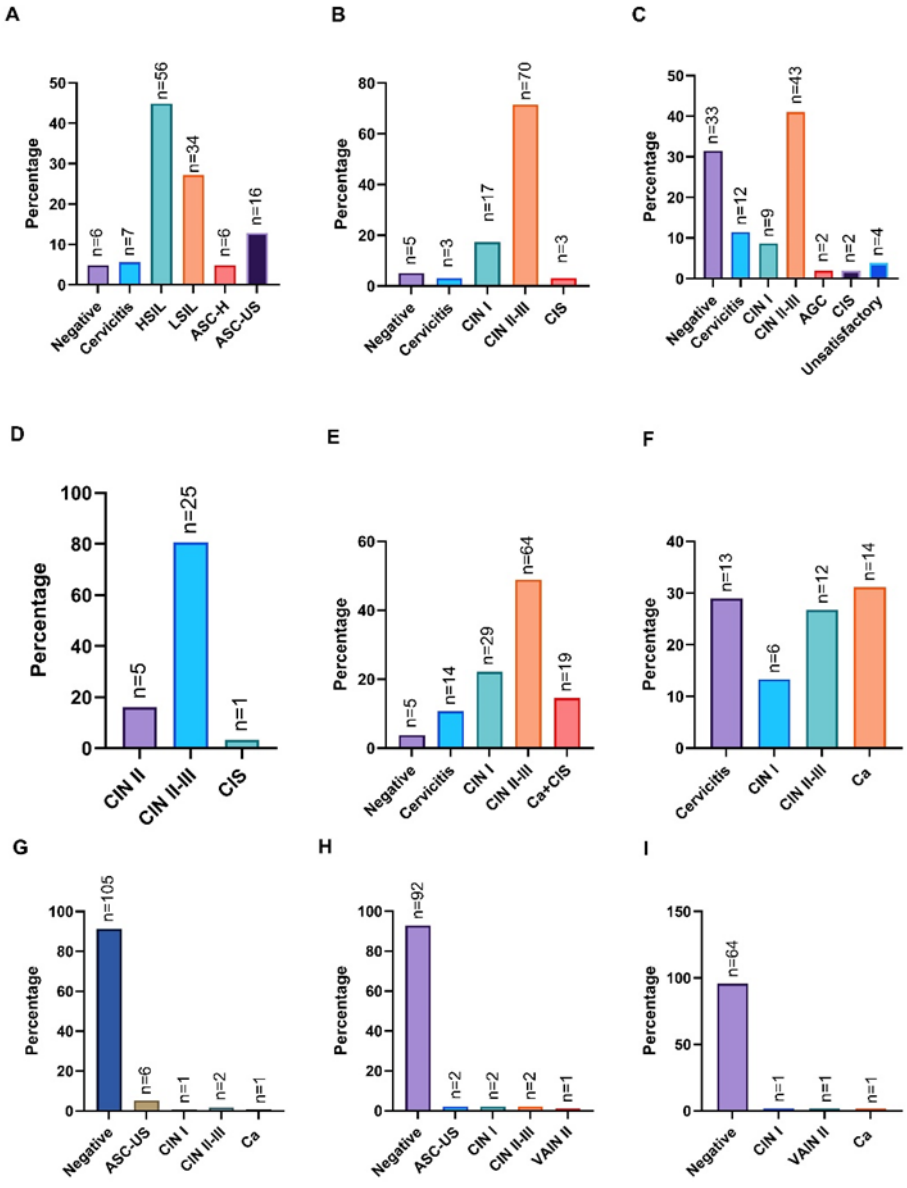

Figure 1. A. Distribution of FPRs; B. Distribution of CBx; C. Distribution of pathologies of ECC specimens; D. Distribution of biopsy pathologies of LEEP cases; E. Distribution of pathology results of patients who underwent conization; F. Distribution of pathology results of patients who underwent hysterectomy; G. First FPT results; H. 2nd FPT results; I. 3rd FPT results.

Table 1 presents a comparison of CBx and FPRs. CBx results of two patients with negative Pap tests were CIN II-III. Of the 5 patients with seven cervicitis on their FPR, 4 had CIN II-III on CBx.

The comparison of the FPRs and conization results is shown in Table 2. The conization results of 2 patients with negative FPRs were CIN II-III. Three patients with cervicitis in their conization results were CIN II-III. Of the 56 patients whose FPRs were HSIL, 11 had Ca/CIS, 29 had CIN II-III, 9 had CIN I, 5 had cervicitis, and 2 were negative based on conization results. Of the 33 patients whose FPRs showed LSIL, 2 had Ca/ CIS, 19 had CIN II-III, 7 had CIN I, 3 had cervicitis, and 2 were negative based on conization results. Of the 6 patients whose FPRs indicated ASC-H, 1 had Ca/CIS, 2 had CIN II-III, 1 had CIN I, and 2 had cervicitis based on conization results.

Table 3 compares the results of CBx, LEEP, conization, and hysterectomy according to the results of the FPRs of the patients. Of the 6 patients whose FPRs were negative, two had CIN II-III, three had CIN I, and one had cervicitis detected in conization performed for other reasons. One of them underwent a hysterectomy, and the result was CIN II-III. Of the 7 patients whose FPRs came back as cervicitis, 2 were found to have CIN II-III in the results of the conization procedures performed for other reasons. One of them underwent a hysterectomy, and the result was cervicitis. Of 56 patients with HSIL in their FPRs, 13 underwent LEEP, and 1 was found to have CIS. The pathology results of the conization outcomes were as follows: 11 Ca/CIS, 29 CIN II-III, 9 CIN I, 5 cervicitis, and 1 negative. Twenty-five of these cases underwent hysterectomies. The pathology results of their slides were Ca/CIS, 9 were CIN II -III, 3 were CIN I, and 5 were cervicitis. Among the 34 patients whose FPRs were LSIL, 2 had a conization result of Ca/CIS. Seven underwent hysterectomies, and 1 of them had a result of Ca/CIS. The conization result of 1 patient with ASC-H smear was Ca/CIS. Interestingly, the conization result of one patient whose FPR was ASC-US was Ca/CIS; this patient underwent a hysterectomy, and the pessary result was the same.

Table 1. Distribution of results of colposcopic biopsy and first Pap test results.

			Biopsy		
First Pap test	**Negative** n (%)	**Cervicitis** n (%)	**CIN I** n (%)	**CIN II-III** n (%)	**Ca/CIS** n (%)
Negative	2 (40.0)	0 (0)	2 (11.8)	2 (2.9)	0 (0)
Cervicitis	0 (0)	0 (0)	1 (5.9)	4 (5.9)	0 (0)
HSIL	1 (20.0)	1 (33.3)	3 (17.6)	33 (48.5)	1 (33.3)
LSIL	1 (20.0)	2 (66.7)	6 (35.3)	19 (27.9)	0 (0)
ASC-H	0 (0)	0 (0)	0 (0)	4 (5.9)	1 (33.3)
ASC-US	1 (20.0)	0 (0)	5 (29.4)	6 (8.8)	1 (33.3)
Total	5 (100)	3 (100)	17 (100)	68 (100)	3 (100)

HSIL: High-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion; ASC-H: Atypical squamous cells -cannot exclude high-grade squamous intraepithelial lesion; ASC-US: Atypical squamous cells of undetermined significance; CIN: Cervical intraepithelial neoplasia; Ca/CIS: Carcinoma / Carcinoma in situ.

Table 2. Distribution of results of first Pap test results and conization.

			Conization		
First Pap test	**Negative** n (%)	**Cervicitis** n (%)	**CIN I** n (%)	**CIN II-III** n (%)	**Ca/CIS** n (%)
Negative	0 (0)	1 (7.7)	3 (10.3)	2 (3.2)	0 (0)
Cervicitis	1 (20.0)	1 (7.7)	2 (6.9)	3 (4.8)	0 (0)
HSIL	2 (40.0)	5 (38.5)	9 (31.0)	29 (46.8)	11 (73.3)
LSIL	2 (40.0)	3 (23.1)	7 (24.1)	19 (30.6)	2 (13.3)
ASC-H	0 (0)	2 (15.4)	1 (3.4)	2 (3.2)	1 (6.7)
ASC-US	0 (0)	1 (7.7)	7 (24.1)	7 (11.3)	1 (6.7)
Total	5 (100)	13 (100)	29 (100)	62 (100)	15 (100)

HSIL: High-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion; ASC-H: Atypical squamous cells -cannot exclude high-grade squamous intraepithelial lesion; ASC-US: Atypical squamous cells of undetermined significance; CIN: Cervical intraepithelial neoplasia; Ca/CIS: Carcinoma / Carcinoma in situ.

Table 3. Comparison of CBx, LEEP, conization, and hysterectomy outcomes according to FPRs.

Biopsy under Colposcopic Observation	**Negative** n (%)	**Cervicitis** n (%)	**HSIL** n (%)	**LSIL** n (%)	**ASC-H** n (%)	**ASC-US** n (%)
Negative	2 (33.3)	0 (0)	1 (2.6)	1 (3.6)	0 (0)	1 (7.7)
Cervicitis	0 (0)	0 (0)	1 (2.6)	2 (7.1)	0 (0)	0 (0)
CIN I	2 (33.3)	1 (20)	3 (7.7)	6 (21.4)	0 (0)	5 (38.5)
CIN II-III	2 (33.3)	4 (80)	33 (84.7)	19 (67.9)	4 (80)	6 (46.2)
AGC/CIS	0 (0)	0 (0)	1 (2.6)	0 (0)	1 (20)	1 (7.7)
LEEP	Negative	Cervicitis	HSIL	LSIL	ASC-H	ASC-US
CIN II	0 (0)	1 (50)	2 (16.4)	2 (22.2)	0 (0)	0 (0)
CIN II-III	0 (0)	1 (50)	10 (76.0)	7 (77.8)	3 (100)	3 (100)
Ca/CIS	0 (0)	0 (0)	1 (7.6)	0 (0)	0 (0)	0 (0)
Conization	Negative	Cervicitis	HSIL	LSIL	ASC-H	ASC-US
Negative	0 (0)	1 (14.3)	2 (3.6)	2 (6.1)	0 (0)	0 (0)
Cervicitis	1 (16.7)	1 (14.3)	5 (8.9)	3 (9.1)	2 (33.3)	1 (6.3)
CIN I	3 (50)	2 (28.6)	9 (16.1)	7 (21.2)	1 (16.7)	7 (43.8)
CIN II-III	2 (33.3)	3 (42.9)	29 (51.8)	19 (57.6)	2 (33.3)	7 (43.8)
CA/CIS	0 (0)	0 (0)	11 (19.6)	2 (6.1)	1 (16.7)	1 (6.3)
Hysterectomy	Negative	Cervicitis	HSIL	LSIL	ASC-H	ASC-US
Cervicitis	0 (0)	1 (100)	5 (20)	4 (57.1)	1 (50)	1 (20)
CIN I	0 (0)	0 (0)	3 (12.2)	1 (14.3)	0 (0)	2 (40)
CIN II-III	1 (100)	0 (0)	9 (36.0)	1 (14.3)	0 (0)	1 (20)
CA/CIS	0 (0)	0 (0)	8 (32.0)	1 (14.3)	1 (50)	1 (20)

HSIL: High-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion; ASC-H: Atypical squamous cells - cannot exclude high-grade squamous intraepithelial lesion; ASC-US: Atypical squamous cells of undetermined significance; CIN: Cervical intraepithelial neoplasia; Ca/CIS: Carcinoma / Carcinoma in situ.

DISCUSSION AND CONCLUSION

Cervical cancer is one of the most preventable and treatable malignancies. Yet, it is the fourth most diagnosed cancer in women of reproductive age worldwide, with the highest incidence in resource-limited countries. Cervical cancer can be diagnosed early with pap smear tests and Human papillomavirus (HPV) screening. HPV DNA testing in combination with cervical smear testing has been reported to increase the likelihood of detecting CIN II-III by %35.[7,8] We conducted this study to evaluate the results of CKC, a procedure we have performed more frequently in our clinic in the past.

The study was unable to evaluate HPV DNA due to the limited availability of HPV DNA testing at that time. In our study, the sensitivity and specificity of the cervical smear test alone, without HPV testing, were shown to be low. For example, one of the 14 patients with CIS had ASCUS in the first smear. This suggests that a single smear in management has low reliability and should be used in conjunction with HPV. This is why co-testing is increasingly preferred for screening.[9]

HSIL is a well-characterized precursor lesion of cervical invasive squamous cell carcinoma.[10] In this study, the FPRs of 11 of 15 (73.3%) patients with CA/CIS detected as a result of conization was HSIL. In a systematic review of 27 articles, the mean CIN2+ percentage in women with cytologically detected HSIL was %77.5.[11]

There have been some studies that have investigated the optimal cone size to reduce surgical field positivity. According to the results of these studies, there is no optimal cone size and depth that can be routinely applied to every patient.[12] Our study did not include data on the size of the cones removed, so the positive surgical margin could not be compared to the size and depth of the cones. In this study, all 131 patients had FPT for the first 3 years after conization and hysterectomy, if available. Only 1 patient who had a pathology of adenoid basal carcinoma showed malignant squamous cell carcinoma in her smear test in the 3rd year. One year after treatment, the smear test result was negative. Follow-up smear samples taken from all other patients were either ASC-US or negative, except for a few HSIL cases.

There are few articles on postoperative positive margins. A meta-analysis that included 1596 patients revealed that 200 patients (13%) had lesions at the surgical margins.[13,14] In this study, 25 patients (18.7%) had a positive surgical margin after conization. Compared to other studies, positive surgical margins were more prevalent in our study.[15-17] Among the 25 patients who had a positive surgical margin, two patients underwent re-conization, and 23 patients underwent type 1 or type 2 hysterectomy. In three of them, the conization results were CIN III, and because their surgical margins were positive, a hysterectomy was performed, and the hysterectomy pieces were identified as squamous cell carcinoma. Purut et al. studied the effects of HPV subtypes in patients with positive surgical margins after conization. In our study, HPV could not be evaluated, so we could not comment much on it.[18]

However, when we looked at the first smear test results of the patient, 19 of 25 (76%) patients had HSIL, 3 (12%) had ASC-US, 2 (8%) were negative, and 1 (4%) had ASC-H.

So far, many studies with cold conization have compared cold conization and Loop Electrosurgical Excision. The advantages and disadvantages of each have been compared.[19-21] On the other hand, in our study, we only evaluated cold conization. The status of the surgical margin in a pathological examination can be more appropriately determined by CKC. A thermal artefact remains the main concern of Loop Electrosurgical Excision.[22] It was reported that morbidity was significantly reduced in the Loop Electrosurgical Excision group, the operative time was shortened, blood loss was reduced, the infection rate decreased in the 2nd postoperative week, and the secondary bleeding rate decreased.[23] Thus, the conventional surgical technique has been recently replaced by laser conization and LEEP in many Western countries.[24-26]

Severe bleeding, especially in the postoperative period, is a major complication of CKC.[27,28] We achieved hemostasis with bilateral interrupted vertical sutures placed after packing the cervical crater with Oxycell. In two patients, postoperative bleeding developed, but it was stopped with transaminated tamponade. No additional procedure was required. CKC has the potential to cause cervical incompetence, which subsequently leads to abortion or preterm delivery during the following pregnancy.[29,30] In our study, two patients had a pregnancy after conization. The first one had a cesarean section at 38 weeks, and the other one had a vaginal delivery at 35 weeks with cerclage at 17 weeks.

A limitation of our study was the unavailability of HPV testing in our hospital during that period, resulting in the evaluation of patients solely by smears. As a result, it was not feasible to compare the outcomes of HPV and conization or to subsequently follow HPV. Additional limitations include the study's non-randomized and retrospective procedure, as well as the limited number of patients enrolled in the trial. To validate the effectiveness of this modified conization procedure, it is necessary to conduct a larger-scale, randomized, controlled research.

In conclusion, cold knife conization remains an acceptable option in the treatment of CIN and microinvasive carcinoma of the cervix, and the excellent diagnostic and therapeutic efficacy of cold knife conization is well-known and confirmed. When properly performed, the procedure has a low risk of complications and provides an accurate histological representation of the disease process. It is also curative in most cases. Of course, excellent clinical results still require careful, long-term, and attentive follow-up.

Ethics Committee Approval: The Declaration of Helsinki was followed in the study. Our study was approved by the Non-Interventional Clinical Research Ethics Committee of Kartal Training and Research Hospital (Date:30.05.2017, decision no: 2017/514/108/7).

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

Author Contributions: Concept – ST; Supervision – ST; Materials – ST; Data Collection and/or Processing –ST; Analysis and/or Interpretation – S.T; Writing – ST.

Peer-review: Externally peer-reviewed.

Acknowledgement: I am deeply grateful to my thesis advisor, the late Prof. Dr. Zehra Meltem Pirimoğlu, for guiding, supporting, and teaching me during my gynecology and obstetrics residency. Your teachings and inspiration continue to resonate in my life and work. Thank you endlessly.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):232-239 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):232-239*

Turkish Validity and Reliability of The Mini Service User Recovery Evaluation Scale

Ruhsal ve Manevi İyileşmeyi Değerlendirme Ölçeği Kısa Formu'nun Türkçe Geçerlilik ve Güvenilirliği

[1]Şule DANIŞ, [2]Nevin GÜNAYDIN

[1]Nurse, Ordu State Hospital, Ordu, Türkiye
[2]Ordu University, Faculty of Health Sciences, Department of Psychiatric Nursing, Ordu, Türkiye

Şule Danış: https://orcid.org/0000-0003-4793-2879
Nevin Günaydın: https://orcid.org/0000-0002-5382-6354

ABSTRACT

Objective: The aim of this research is to adapt the Mini-Service User Recovery Evaluation (MiniSeRvE) Scale to Turkish culture and establish its psychometric properties.

Materials and Methods: This methodological study included 150 patients who applied to psychiatry outpatient clinics between March 2020 and January 2021. "The Personal Information Form," "The MiniService User Recovery Evaluation (MiniSeRvE) Scale," "The Subjective Recovery Assessment Scale," and "The Spiritual Well-Being Scale" were used to collect the data.

Results: The CFA of the MiniSeRvE Scale determined that the three sub-dimensions and factor loadings were between 0.50 and 0.91, consistent with the original scale. The Cronbach's alpha coefficient was found to be 0.864 for the total scale and between 0.77 and 0.95 for the sub-dimensions.

Conclusions: The MiniSeRvE Scale is a valid and reliable measurement tool.

Keywords: Mental recovery, reliability, spiritual recovery, validity

ÖZ

Amaç: Bu araştırmanın amacı MiniService İyileşmeyi değerlendirme (MiniSeRvE-Ruhsal ve Manevi İyileşmeyi Değerlendirme Ölçeği) Ölçeği'nin Türk kültürüne uyarlanması ve psikometrik niteliklerinin ortaya konulmasıdır.

Materyal ve Metot: Bu metodolojik çalışmaya psikiyatri polikliniklerine Mart 2020-Ocak 2021 tarihleri arasında başvuran 150 hasta dahil edilmiştir. Veri toplamak için "Kişisel Bilgi Formu", "Ruhsal ve Manevi İyileşmeyi Değerlendirme Ölçeği (MiniSeRvE) ", "Öznel İyileşmeyi Değerlendirme Ölçeği" ve "Spiritüel İyilik Ölçeği" kullanılmıştır.

Bulgular: MiniSeRvE Ölçeğinin DFA analizi sonucunda üç alt boyutun ve faktör yüklerinin orijinal ölçekte olduğu gibi 0,50 ile 0,91 arasında olduğu belirlendi. Cronbach alfa katsayısı ölçeğin tamamı için 0,864, alt boyutları için ise 0,77-0,95 arasında bulunmuştur.

Sonuç: Ruhsal ve Manevi İyileşmeyi Değerlendirme Ölçeği, geçerli ve güvenilir bir ölçme aracıdır.

Anahtar Kelimeler: Geçerlilik, güvenirlik, ruhsal iyileşme, spiritüel iyileşme

Sorumlu Yazar / Corresponding Author:
Nevin Günaydın
Department of Psychiatric Nursing, Health Sciences Faculty, Ordu University, Cumhuriyet Yerleşkesi, Ordu, Türkiye
Tel: +905057673752
E-mail: nevin_altintas@yahoo.com.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 18/03/2024
Kabul Tarihi/ Accepted: 19/07/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Danış Ş and Günaydın N. Turkish Validity and Reliability of The Mini Service User Recovery Evaluation Scale. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):232-239. doi: 10.26453/otjhs.1454819

INTRODUCTION

Recovery is a process that enables a person to use their current potential in the best way, to participate in practices that will protect and improve their health.[1] Recovery from mental illnesses is a process rather than an outcome.[2]

Recovery is the process of discovering new meaning and purpose in life as an individual. It is critical to remember that it implies a decision to develop a life beyond the illness.[3] However, people with SPMI (severe and persistent mental illness) face unique challenges in finding meaning in life and establishing a new existence outside of psychiatric treatment. They remain defenceless in dealing with these issues.[4]

One of the most important factors that affect recovery and support the process of finding meaning in life is the concept of "spirituality". Most of the data obtained show that spirituality/ practices contribute positively to the recovery process.[5,6] Seeing spirituality as a source of power, considering spiritual values and using spirituality to eliminate sources of stress demonstrates that health, recovery, and spirituality are integral.[7]

There are multiple measurement tools used to evaluate recovery in the national literature.[8-11] However, a scale including the subject of spirituality was not found among these scales. This scale, which evaluates spirituality and recovery, will be able to objectively assess the subjective concepts of "recovery in mental illnesses and spirituality." It is expected that the results of this study will contribute to the treatment and care management of individuals with mental health problems.

The purpose of this study is to test the validity and reliability of the Mini-SeRvE scale in Turkish.

MATERIALS AND METHODS

Ethical Considerations*:* Research permission was obtained from the Ordu Provincial Health Directorate (Date: 29.09.2020, decision no: 66501263-535324) and approval from the Ordu University Clinical Research Ethics Committee (Date: 30.01.2020, decision no: 2020-15) were obtained for the study. Written informed consent was obtained from the participants.

Type of Study: This study was carried out methodologically to adapt the Mini Service User Recovery Evaluation Scale (Mini-SeRvE) into Turkish and to ensure its validity and reliability.

Participants in the study were those who applied to a University Training and Research Hospital and a State Hospital Psychiatry outpatient clinic, were diagnosed with depression, and had been treated for at least six months. Of these individuals, 150 outpatients satisfied the inclusion requirements and were chosen using the unlikely sampling technique. Since Akgul stated that the number of items should be 5-10 times higher when determining the sample size,[11] 150 depressive patients were reached in this study, whose item number was ten times that of the items (15 items).

People who are over 18 years old, literate, have no acute physical illness, have been diagnosed with depression at least six months ago according to DSM-V, and have no known neurocognitive disorders were accepted into the study.

The data of the study were collected with the Personal Information Form created by compiling the literature, "The Spiritual Well-Being Scale,[12]" "The Mini Service User Recovery Evaluation Scale (Mini -SeRvE),[13]" "The Subjective Recovery Evaluation Scale (SubRAS)[10]" and "The Personal Information Form."

Data Collection Tools:

***The Personal Data Form*:** The personal data form consists of 15 items, including the sociodemographic characteristics of the participants and the characteristics of the disease/treatment.[9,10,12,13]

***The Spiritual Well-Being Scale*:** The 29-item scale developed by Ekşi and Kardaş was prepared in a 5-point Likert type.[12] Scoring of the scale consists of three sub-dimensions. The total Cronbach's Alpha value (0.886) and the subscales (0.853-0.953) were determined for the original scale. In this study, the total Cronbach's Alpha value (0.886) and the subdimension values (0.776-0.949) were found.

***The Mini Service User Recovery Evaluation Scale (Mini-SeRvE*):** Mini-SeRvE, developed by Barber et al., in a 5-point Likert type. It is a 15-item scale used to evaluate the recovery levels of individuals subjectively.[13] It includes three subscales. The total Cronbach's alpha value (0.852) and the subscales (0.756-0.848) were determined for the original scale. As a result of the Turkish validity and reliability study, Cronbach's alpha values for the subscales were found to be 0.773-0.953.

The Subjective Recovery Evaluation Scale (SubRAS): SubRAS, developed by Yıldız et al. to evaluate subjective recovery in schizophrenia patients, consists of 17 items.[10] The scale uses a 5-point Likert-type format, with a Cronbach's alpha coefficient of 0.98. The item-total score correlation coefficients were calculated to range between 0.83 and 0.94. In this study, the Cronbach's alpha coefficient of the scale was found to be 0.862.

The Mini Service User Recovery Evaluation Scale: Turkish Adaptation, Validity and Reliability Process (Mini-SeRvE)

Language Validity: The scale was initially translated from English to Turkish by two academicians to ensure language equivalence of the Mini-SeRvE

scale. The Turkish version of the form was then translated back into English by a linguistics expert fluent in both languages and cultures. The Turkish version was finalized after necessary corrections were made in consultation with the scale's developer.Formun Üstü

Content Validity (CVI): After confirming the Mini-SeRvE scale's language validity, the opinions of multiple experts were sought for content validity.[14] Following their recommendations, the CVI of all scale items was evaluated by 12 academics using the Davis technique[15]. The CVI scores for all items on the scale were found to be above 0.83, and no items needed to be removed from the scale.

Pilot Study: The final version of the scale was administered to a group of 20 individuals with characteristics similar to those of the main research sample but who were not part of the primary study. These participants were asked to assess the items for clarity, relevance, and readability. The final form of the scale was then adjusted as necessary based on their feedback.

Construct Validity: Construct validity is used to determine theoretical and practical compatibility.[16] In this study, the Kaiser-Mayer Olkin (KMO) index (0.817), Bartlett's test ($\chi 2$= 1202.267, p= 0.000), and anti-image correlations indicated that the data were sufficiently correlated and suitable for factor analysis.[11] Also, in the validity and reliability study of the Mini-SeRvE Scale, there was found statistically significant, positive, and moderate correlation with parallel form (the Spiritual Well-Being Scale) scores (Rho coefficient= 0.739, p< 0.05) (r-value ranges: 0-0.49.9: low, 0.50-0.74.9: moderate, 0.75-1.00: high).

Statistical Analysis: SPSS 22.00 statistical package program and AMOS 24 were used to evaluate the research data. First, Bartlett's sphericity test and the KMO sampling adequacy test were employed to gauge the sample size's suitability. The literature states that the KMO result must be over 0.50/0.60-1.00 for the sample to be considered legitimate, and the closer it is to 1, the more significant the finding.[17-19] Bartlett's sphericity test value for the correlation matrix should be p< 0.05, and the power analysis value for calculating the sampling power should be over 80%.[20] The Mini-SeRvE scale was first tested for validity. For this purpose, construct validity and criterion-related validity tests were conducted. Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA) were used to test construct validity.[17] Additionally, EFA was applied to the scale items. Also, p<0.05 was accepted as a significance value. Model adequacy was assessed using the Comparative Fit Index (CFI), Goodness of Fit Index (GFI), Adjusted Goodness of Fit Index (AGFI), Normed Fit Index (NFI), Standardized Root Mean Square Residual (SRMR), Mean Squared Error of Approximation (MSE), and chi-square statistics (χ^2/ df) as acceptable indicators of fit.[18,20,21] For criterion -related validity, Spearman's Rho coefficient and Pearson product-moment correlation coefficient (r) were used for statistical analysis. For the reliability of the scale, the internal consistency of the scale and subscales were evaluated using item-total correlations and Cronbach's alpha reliability coefficient.[22]

RESULTS

Women agreed to participate in the study in 70% of cases. Among the participants, 34.7% were high school graduates, 63.3% were married, 64% had children, 59.3% of the participants did not have a diagnosed physical or chronic disease, and 49.3% rated the level of social support received from their family as "high". The mean time since diagnosis was 67.14±74.67 months (Table 1).

Table 1. Descriptive Characteristics of Participants.

		n (%)
Gender	Female	105 (70)
	Male	45 (30)
Level of Education	Literate	7 (4.7)
	Primary School	24 (16)
	Middle School	21 (14)
	High School	52 (34.7)
	University	46 (30.7)
Job	Unemployed	83 (56.5)
	Officer	28 (19)
	Employee	21 (14.3)
	Self-employment	5 (3.4)
	Retired	10 (6.8)
Habits	Not using	77 (51.3)
	Alcohol	6 (4)
	Cigarette	54 (36)
	Substance use	1 (0.7)
	Both	12 (8)

Table 1. Continue.

Marital Status	Married		95 (63.3)
	Single		44 (29.3)
	His wife passed away		6 (4)
	Divorced		5 (3.3)
Having Children	Yes		96 (64)
	No		54 (36)
Income Rate	Low		35 (23.3)
	Middle		110 (73.3)
	High		5 (3.3)
Diagnosed Physical or Chronic Illness	Yes		61 (40.7)
	No		89 (59.3)
Using a Source Other Than Medical Treatment	Yes		22 (14.7)
	No		128 (85.3)
Social Support From Family	Low		35 (23.3)
	Middle		41 (27.3)
	High		74 (49.3)
Social Support From Friends	Low		22 (14.7)
	Middle		71 (47.3)
	High		57 (38)
Social Support From Doctor	Low		8 (5.3)
	Middle		75 (50)
	High		67 (44.7)
	n	**Min-Max**	**Mean**
Age	150	18.00-78.00	38.32±13.64
Number of Children	116	0-6.00	1.76±1.12
Diagnostic Time	150	6.00-420.00	67.14±74.67
Treatment Time	150	6.00-420.00 *	63.90±75.38

*: The duration of treatment is given in months.

When Table 2 is examined, it is seen that the Mini-SeRvE scale consists of three sub-dimensions, similar to the original structure. The factor loads of all items of the scale are above 0.40, and the explained variance is 61.724% for the Total Mini-SeRvE Scale. Therefore, no items were removed from the scale at this stage, and a 3-dimensional structure was accepted (Table 2).

Table 2. Factor Analysis of the Mini-SeRvE Scale.

Item no	**Items**	**Factor/Sub-Dimension**		
		Existential Well-Being	**Religious Well-Being**	**Mental Ill-Being**
1.	I have hope for the future.	**0.706**	0.180	0.100
3.	I am confident I can cope with most things in life.	**0.524**	0.291	0.234
5.	I feel a sense of meaning and purpose in life	**0.757**	0.024	0.115
6.	I can find or create something beautiful in life	**0.845**	0.153	0.101
8.	I can accept myself	**0.503**	0.276	0.284
10.	I believe in my ability to overcome my problems	**0.724**	0.272	0.224
2.	I am upset by the stigma or shame of my problems	-0.003	0.046	**0.795**
4.	I feel agitated	0.269	-0.111	**0.558**
7.	I feel other people against me.	0.176	-0.039	**0.638**
9.	I have lost inner motivation	0.475	-0.114	**0.672**
11.	I feel isolated or cut off from others	0.195	0.328	**0.528**
13.	My faith/spiritual belief gives me difficult thoughts	0.033	0.403	**0.728**
12.	My faith/spiritual belief is helpful to me	0.284	**0.897**	0.076
14.	I find it helpful to attend religious services or do religious rituals.	0.144	**0.911**	-0.015
15.	I find it helpful to pray	0.238	**0.912**	0.038
Explained Variance (%)		22.424	20.377	18.923
Total Explained Variance (%)			**61.724**	

Structural equation modelling was then established with CFA to obtain more precise results after EFA. Based on the relevant fit index values, it was decided that the model was acceptable as it is (Table 3).

The sub-dimensions of the Mini-SeRvE Scale and the factor loads of the items are presented in the form of a PATH diagram. As seen in Figure 1, the model was accepted in its original structure without any modifications. The t-value for all items is above 1.96 (ranging from 2.49 to 10.90). No modifications were applied to improve the model (Figure 1).

The distribution of the lowest and highest scores, mean scores, and Cronbach's alpha values obtained from the Mini-SeRvE Scale and its sub-dimensions are presented in Table 4.

Table 3. Adjustment Index Values, Normal and Acceptable Values for the Mini Service User Recovery Evaluation Scale.

Index	Normal value	Acceptable value	Value found
x^2/SD	<2	<5	1.65
GFI	>0.95	>0.90	0.96
AGFI	>0.95	>0.90	0.95
CFI	>0.95	>0.90	0.99
RMSEA	<0.05	<0.08	0.067
SRMR	<0.05	<0.08	0.084

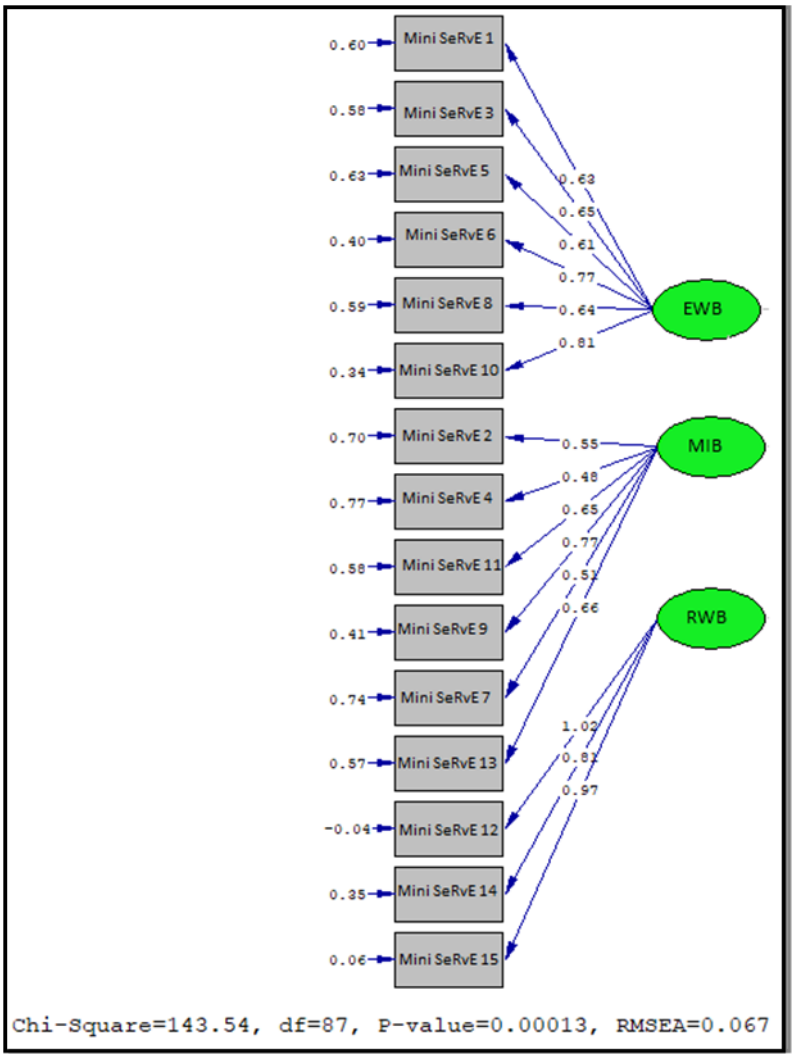

Figure 1. PATH Diagram for the Factor Structure of the Mini-SeRvE Scale.

Table 4. Scores Received from the Mini Service User Recovery Evaluation Scale and its Sub-Dimensions.

	n	Min	Max	Mean	SD	Cronbach alfa
Existential Well-being	150	7.00	30.00	22.61	6.16	0.839
Mental Ill-being	144	6.00	30.00	22.96	5.93	0.773
Religious Well-being	144	3.00	15.00	13.10	3.11	0.953
Total of Mini SeRvE Scale	144	19.0 0	75.00	58.93	11.82	0.864

DISCUSSION AND CONCLUSION

This part of the study discusses the findings on language validity, content validity, construct validity, and internal consistency of the Mini-SeRvE scale.

In this study, content validity was evaluated using the Davis method. A CVI value of 0.80 is considered the threshold.[18] After translating the scale into Turkish, the adapted scale items should be evaluated for content validity by at least 3 and up to 20 experts.[23] In this study, the CVI value exceeded 0.83, and no items were removed from the scale.

Construct validity evaluates the intangible qualities of a scale, including how accurately these qualities are measured, alongside its reliability and validity.[24] A high level of construct validity indicates high agreement between items and their homogeneity.[21,22] Prior to conducting factor analysis, it is essential to assess the adequacy of the sample size. In this study, KMO (0.817) and Bartlett's tests (χ^2=1202.267, p=0.000) were performed for this purpose. Values above 0.50 are considered acceptable for anti-image correlation.[19,25] In this study, all anti-image correlation values were above 0.50. Upon evaluating the test results, it was observed that the sample follows a normal distribution, the data are consistent, and the sample is suitable for factor analysis.

As a result of the EFA of the Mini-SeRvE scale, it was found that the factor loads of the three sub-dimensions ranged from 0.503 to 0.912, and all item factor loads were higher than the accepted value of 1.96 ($p< 0.05$).[17] Therefore, no items were removed from the scale. Furthermore, the total variance explained by the three-dimensional structure, 61.724%, indicates sufficient factor loads of the items and adequate variance explained, making the scale suitable for use in Turkish culture in its three-dimensional structure, similar to the original. These EFA results were found to be comparable to those of a study conducted in Australia.[26]

Confirmatory factor analysis (CFA) evaluates the significance level between observed variables and the proposed structure.[20] According to literature standards, the following values are expected: SRMR (values close to zero between 0 and 1), RMSEA (below 0.08), CFI (expected to be above 0.85-0.95), GFI and AGFI (good model indicators above 0.90), and χ^2/df (should be below two, with values below five considered acceptable)[27]. In this study, the χ^2/df value was 1.65, GFI was 0.96, AGFI was 0.95, CFI was 0.99, RMSEA was 0.067, and SRMR was 0.084, confirming the adequacy of the model. This aligns with the acceptable range reported in previous studies conducted in Türkiye (GFI=0.98, AGFI=0.77, CFI=0.80, RMSEA=0.07)[12] and Australia (GFI=0.81, AGFI=0.77, CFI=0.80, RMSEA=0.08).[26] Therefore, it can be concluded that the 3-factor structure of the Mini-SeRvE scale, consisting of 15 items, is suitable for the model and demonstrates construct validity similar to its original version.

Internal consistency refers to the extent to which all subsections of the scale measure the same construct.[28] A Cronbach's alpha coefficient of 0.70 and above indicates reliability, with values of 0.80 and above indicating high reliability.[17,19] In this study, the Cronbach's alpha coefficient of the total scale (0.864), 'Existential Well-Being' sub-dimension (0.839), 'Mental Ill-being' sub-dimension (0.773), and 'Religious Well-Being' sub-dimension (0.953) were calculated. In the original version of the scale, the total Cronbach's alpha value (0.852) for "Existential Well-Being (0.848)", for "Mental Ill-being (0.761)", and for "Religious Well-Being (0.756)", sub-dimensions were similar.[10] Therefore, it can be concluded that the scale demonstrates high reliability.

Two different parallel forms were utilized: the "Subjective Recovery Evaluation Scale (0.739, $p< 0.001$)" for mental recovery and the "Spiritual Well-Being Scale (0.541, $p< 0.001$)" for spiritual recovery. These values indicate a satisfactory level of correlation between the two forms. Additionally, it was found that the total score of the Mini-SeRvE scale explained 61.724% of the variance. In a study where the parallel form was used in scale adaptation, a positive, moderately statistically significant relationship was found between the two scales used ($r=0.686$, $p< 0.001$).[29]

In conclusion, the Mini-SeRvE scale subjectively evaluates mental and spiritual recovery among patients, was successfully adapted to Turkish and validated as a reliable measurement tool suitable for Turkish culture. This research fills a significant gap in the Turkish literature concerning recovery and spirituality, providing a validated measurement tool. It serves as a foundational resource for future studies and applications in clinical settings.

Ethics Committee Approval: This study was approved by the Ordu University Clinical Research Ethics Committee (Date: 30.01.2020, decision no: 2020-15). This study was conducted by the principles of the Declaration of Helsinki.

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

Author Contributions: Concept – ŞD, NG; Supervision – NG; Materials – ŞD; Data Collection and/or Processing – ŞD; Analysis and/or Interpretation – ŞD, NG; Writing –ŞD, NG.

Peer-review: Externally peer-reviewed.

Acknowledgement*:* We thank the participants in our study.

Other Information: This study was produced from the master's thesis entitled "Turkish Validity and Reliability of The Mini Service User Recovery Evaluation Scale". This study was presented as an oral presentation at the V. International X. National Psychiatric Nursing Congress, 20-23 Ekim 2021, İzmir.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):240-245 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):240-245*

Diagnostic Value of Neutrophil/Lymphocyte Ratio in Distinguishing Peripheral and Central Vertigo in Patients with Dizziness

Baş Dönmesi Olan Hastalarda Periferik ve Santral Vertigonun Ayırt Edilmesinde Nötrofil/Lenfosit Oranının Tanısal Değeri

[1]İskender SERTBAŞ, [2]Mustafa ÇİÇEK, [3]Metin YADİGAROĞLU, [4]Sinan PASLI, [5]Selman YENİOCAK, [4]Abdulkadir GÜNDÜZ

[1]Fatih State Hospital, Emergency Clinic, Trabzon, Türkiye
[2]University of Health Sciences, Trabzon Kanuni Training and Research Hospital, Clinic of Emergency Medicine, Trabzon, Türkiye
[3]Samsun University Faculty of Medicine, Department of Emergency Medicine, Samsun, Türkiye
[4]Karadeniz Technical University, Faculty of Medicine, Department of Emergency Medicine, Trabzon, Türkiye
[5]University of Health Sciences, Haseki Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Türkiye

İskender Sertbas: https://orcid.org/0000-0001-9948-3716
Mustafa Çiçek: https://orcid.org/0000-0003-4307-3261
Metin Yadigaroğlu: https://orcid.org/0000-0003-1771-5523
Sinan Paslı: https://orcid.org/0000-0003-0052-2258
Selman Yeniocak: https://orcid.org/0000-0002-1124-396X
Abdülkadir Gündüz: https://orcid.org/0000-0001-8591-9769

ABSTRACT

Objective: Neutrophil/lymphocyte ratio (NLR) is an inexpensive parameter that gives an idea about systemic inflammatory response and cellular immune response. This study aims to investigate the value of NLR in distinguishing peripheral and central vertigo.

Materials and Methods: Patients presenting with acute vertigo at the emergency clinic were included between January 2017 and December 2018. Hemogram, brain computerized tomography, and diffusion magnetic resonance imaging data were reviewed to categorize patients into peripheral and central vertigo groups. Laboratory parameters were compared between these groups.

Results: Neutrophil, lymphocyte, and C-reactive protein levels were higher in patients with central vertigo than those with peripheral vertigo (p=0.003, p=0.003, p=0.022, respectively). Moreover, the NLR value was significantly elevated in central vertigo cases (median: 3.99) in contrast to peripheral vertigo cases (median: 2.32) (p <0.001).

Conclusions: The NLR is a valuable marker for distinguishing peripheral and central vertigo in emergency department patients with dizziness. Higher NLR values suggest central vertigo.

Keywords: Emergency department, differential diagnosis, dizziness, neutrophil/lymphocyte ratio, vertigo

ÖZ

Amaç: Nötrofil/lenfosit oranı (NLR), sistemik inflamatuar yanıt ve hücresel bağışıklık yanıtı hakkında fikir veren düşük maliyetli bir parametredir. Bu çalışmanın amacı, NLR'nin periferik ve merkezi vertigo arasındaki farkı ayırt etmedeki değerini araştırmaktır.

Materyal ve Metot: Ocak 2017 ile Aralık 2018 tarihleri arasında acil klinikte akut vertigo ile başvuran hastalar çalışmaya dahil edildi. Hastaları periferik ve merkezi vertigo gruplarına ayırmak için hemogram, beyin bilgisayarlı tomografi ve difüzyon manyetik rezonans görüntüleme verileri incelendi. Laboratuvar parametreleri bu gruplar arasında karşılaştırıldı.

Bulgular: Nötrofil, lenfosit ve C-reaktif protein düzeyleri, periferik vertigo hastalarına kıyasla merkezi vertigo hastalarında daha yüksek bulundu (sırasıyla p=0,03, p=0,003, p=0,022). Ayrıca, NLR değeri merkezi vertigo vakalarında (ortalama: 3,99), periferik vertigo vakalarına kıyasla (ortalama: 2,32) anlamlı derecede yüksekti (p <0,001).

Sonuç: NLR, vertigo semptomlarıyla acil servise başvuran hastalarda periferik ve merkezi vertigo arasındaki farkı ayırt etmede değerli bir belirleyicidir. Yüksek NLR değerleri merkezi vertigoyu düşündürmektedir.

Anahtar Kelimeler: Acil servis, ayırıcı tanı, baş dönmesi, nötrofil/lenfosit oranı, vertigo

Sorumlu Yazar / Corresponding Author:
Metin Yadigaroğlu
Mevlana District Bornova Avenue Megacity Apartment No:81
Flat:28 Atakum/Samsun, Türkiye
Tel: +905367818888
E-mail: metin.yadigaroglu@samsun.edu.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 31/03/2024
Kabul Tarihi/ Accepted: 03/08/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Sertbaş İ and et al. Diagnostic Value of Neutrophil/Lymphocyte Ratio in Distinguishing Peripheral and Central Vertigo in Patients with Dizziness. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):240-245. doi: 10.26453/otjhs.1461279

INTRODUCTION

Peripheral vertigo (PV) occurs in the vestibular labyrinth with nerve damage.[1] Central vertigo (CV) mainly occurs due to mortal causes such as brain stem and cerebellum strokes, and transient ischemic attack.[2] For this reason, it is vital to distinguish PV or CV in patients who present to the emergency department reporting vertigo. In patients presenting with vertigo symptoms and findings, although anamnesis and physical examination are valuable to distinguish PV or CV, advanced radiologic examinations such as brain computed tomography (BCT) and diffusion magnetic resonance imaging (MRI) are often required.[3]

During stress and inflammatory response, there is an increase in circulating neutrophil cell ratios. The neutrophil/lymphocyte ratio (NLR) is an easy-to-obtain, inexpensive parameter that gives an idea about the systemic inflammatory response and cellular immune response and is considered an inflammatory response indicator.[4,5] In acute ischemic stroke or hemorrhagic stroke, the inflammatory response increases due to post-ischemic changes and brain damage, and NLR is expected to increase.[6,7] Additionally, there are studies indicating an elevation in NLR levels among patients with PV.[8,9]

There is currently no literature evaluating NLR levels in distinguishing between PV and CV. Therefore, we aimed to investigate the value and applicability of NLR in the differential diagnosis of PV and CV.

MATERIALS AND METHODS

Ethics Committee Approval: Our study was approved by the Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 31.05.2019, decision no: 24237859-439). During the study, the Helsinki Declaration criteria were complied with to protect the patient's data.

Study Design and Setting: This was a single-center, retrospective, and cross-sectional study conducted in the emergency department of a tertiary university hospital to which 95,000 patients present annually. Patients who presented to the emergency medicine clinic reporting dizziness over two years between Jan 1st, 2017, and Dec 31st, 2018, were included in the study. Patients with trauma, those with an additional acute infectious disease, patients with malignancy, those with chronic inflammatory disease, patients aged under 18 years, and patients without complete blood counts were excluded from the study. Additionally, among the patients included in the PV group, those who presented to the emergency department with any infection/inflammatory disease that altered NLR, any otologic disease, or central nervous system pathologies within the following 1-week period were excluded from the study. According to the International Classification of Diseases-10th version (ICD-10) coding system of the emergency department, the file and computer records of patients aged 18 years and over who had an ICD-10 code for vertigo (R.42) were examined, and the results of hemograms, BCT, and MRI were evaluated.

Participants: The BCTs and diffusion MRIs of patients who presented to the emergency department with dizziness were examined. In these images, patients without cerebral pathology (ischemia, infarction, hemorrhage, mass) were diagnosed as having PV. A group of patients diagnosed as having CV was established with patients with cerebral pathology in their imaging. The files and computer records of the patients included in the study were examined, and parameters such as sex, age, the presence of symptoms accompanying the vertigo attack, other diseases, platelet count, leukocyte count, neutrophil count, lymphocyte count, and NLR were recorded as indicated in the patient registration form.

Statistical Analysis: IBM SPSS Statistics 25 package program used for data analysis. Descriptive statistics are given as numbers and percentages for categorical variables in the statistical analysis of the data. Mean and standard deviation are given for parametric data for numerical variables, and median, minimum, maximum and interquartile ranges are given for non-parametric data. The independent sample t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data to compare numerical variables in two independent groups. The receiver operating characteristics (ROC) analysis was used to determine the cut-off value of the NLR. Results of the ROC analysis were given with 95% confidence intervals (CI) and the area under the curve (AUC). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 282 patients who were diagnosed as having vertigo in the study period were retrospectively screened. Twenty-two patients were excluded from the study. Twelve patients were excluded from the study due to infection/inflammatory disease, five patients were found to have malignancy, three patients had gastrointestinal bleeding, and a complete atrioventricular block was detected in two patients (Figure 1). A total of 260 patients were included in the study. These patients were divided into PV and CV according to their history, physical examinations, and brain CT and MRI results.

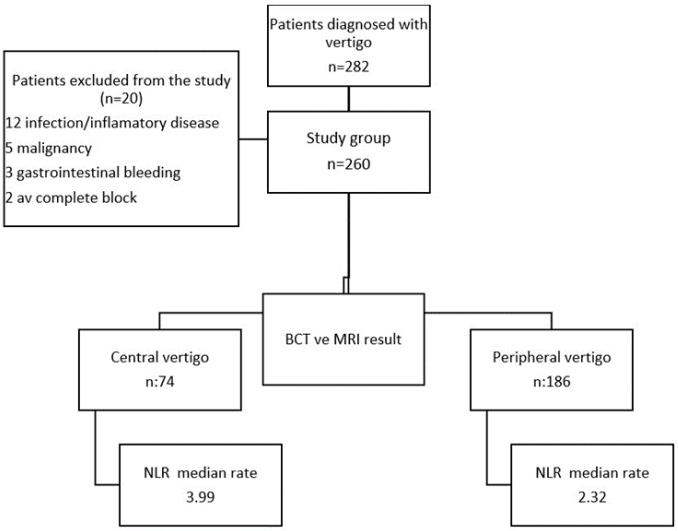

Figure 1. Study flow chart.

While 186 patients (71.5%) were diagnosed with CV, 74 (28.5%) were diagnosed with PV. Sociodemographic characteristics, comorbidities, and presenting symptoms were compared between patients with PV and CV (Table 1). More female patients were diagnosed with both PV and CV compared to male patients, although the difference was not statistically significant (p=0.166). The median age of patients with CV was 72.5 years (range: 20-100 years), while the median age of patients diagnosed with PV was 62.0 years (range: 18-93 years), with a statistically significant difference observed (p <0.001). 113 (43.5%) patients had hypertension (HT), 54 (20.8%) had atrial fibrillation (AF), 49 (18.8%) had diabetes mellitus (DM), 18 (6.9%) had a history of previous stroke, and 17 (6.5%) had coronary artery disease (CAD). The incidence of HT and CAD was significantly higher in patients with CV compared to those with PV (p <0.001 and p=0.027, respectively). Although the prevalence of AF and a history of stroke was higher in CV patients, and DM was more common in PV patients, these differences were not statistically significant. The frequency of nausea-vomiting (65.1%), and nystagmus (31.2%) were statistically significantly higher in patients with PV than in patients with CV (p <0.001). The frequency of hemiplegia (n=8, 10.8%), hemiparesis (n=20, 27.0%), speech impairment (n=17, 23.0%), facial asymmetry (n=1, 1.4%), and tinnitus (n=5, 6.8%) was found to be much higher in patients with CV (p <0.001).

Table 1. Sociodemographic characteristics, comorbidities, and presenting symptoms of the patients.

		Central vertigo	Peripheral vertigo	p-value
Gender,	Male	36 (48.6)	73 (39.2)	0.166
	Female	38 (51.4)	113 (60.8)	
n (%)	Age (years), median (IQR)	72.5 (100)	62 (93)	**0.001**
Comorbidities,	Hypertension	47 (63.5)	66 (35.5)	**0.001**
n (%)	Atrial fibrillation	21 (28.4)	33 (17.7)	0.082
	Diabetes mellitus	13 (17.6)	36 (19.4)	0.875
	Previous stroke	8 (10.8)	10 (5.4)	0.198
	Coronary Artery Disease	9 (12.2)	8 (4.3)	**0.027**
Symptoms, n	Hemiplegia	8 (10.8)	1 (0.5)	**0.001**
(%)	Hemiparesis	20 (27)	2 (1.1)	**0.001**
	Speech disorder	17 (23)	-	**0.001**
	Facial asymmetry	1 (1.4)	-	**0.001**
	Nausea-vomiting	34 (45.9)	121 (65.1)	**0.001**
	Tinnitus	5 (6.8)	3 (1.6)	**0.001**
	Nystagmus	8 (10.8)	58 (31.2)	**0.001**

Table 2 shows the laboratory findings of patients with PV and CV. The median leukocyte, neutrophil, and CRP values of patients with CV were statistically significantly higher than in patients with PV ($p < 0.05$). In addition, the median lymphocyte value was found to be higher in patients with PV than in those with CV ($p < 0.05$). In terms of median hemoglobin values, there was no significant difference between patients with PV and CV ($p > 0.05$). The median NLR (median: 3.99) of patients with CV was significantly higher than the median NLR (median: 2.32) of patients with PV ($p < 0.001$).

Table 3 and Figure 2 demonstrate the ROC analysis used for the threshold value calculation used to separate PV and CV. According to the results, the area under the receiver operating characteristic (ROC) curve was found as 0.679 (95% CI: 0.600-0.757), which was statistically significant in diagnosis.

Table 2. Laboratory findings of patients.

Laboratory findings	Central vertigo Median	Min.	Max.	IQR	Peripheral vertigo Median	Min.	Max.	IQR	p-value
Leukocyte	8680.0	3690	24150	5165	7550.0	3650	13950	2970	**0.003**
Neutrophil	5745.0	2120	22210	4398	4570.0	1250	11580	2223	**0.003**
Lymphocyte	1580.0	180	8520	1158	2035.0	500	6760	1275	**0.003**
Hb (gr/dL)	14	8.8	16.9	2.55	13.3	9.7	18.5	1.90	0.323
NLR	3.99	0.54	65.61	4.17	2.32	0.29	12.79	2.06	**0.001**
CRP	0.55	0.01	30.00	1.23	0.25	0.01	5.30	0.50	**0.022**

Table 3. ROC analysis of patients' neutrophil/lymphocyte ratio.

	Cutoff Value	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUC p-value
NLR	3.25	62,16% 95% CI (50.1-73.2)	72,58% 95% CI (65.6-78.9)	2.27	0.52	0.679 **0.001**

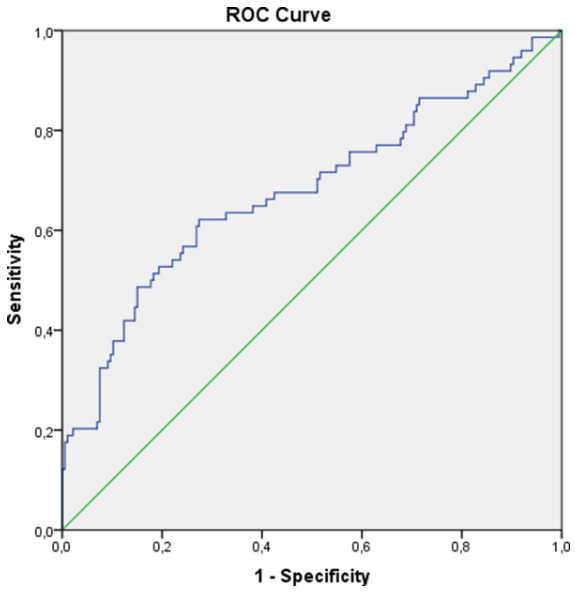

Figure 2. ROC curve for Neutrophil/lymphocyte ratio in the distinguishing of vertigo types.

DISCUSSION AND CONCLUSION

The median NLR was statistically significantly higher in patients with CV than those with PV. Therefore, it can be thought that NLR can be used as a parameter in the differential diagnosis of PV and CV. In the study conducted by Lee et al. on 135 patients, the authors recommended MRI for further investigations if NLR >2.8 to find out ischemic stroke.[10] Çelikbilek et al. found that NLR was higher in patients with atherothrombotic acute ischemic stroke than in patients with transient ischemic attacks and controls.[11] The study conducted by Tokgöz et al. supported that a high NLR could be used as an independent indicator for predicting short-term deaths in patients with acute ischemic stroke.[12] Our results are compatible with the literature.

In the studies on vertigo, the incidence increased with age, especially in women. It has been found that benign paroxysmal positional vertigo, Meniere's disease, and migrainous vertigo are more common in women than in men.[13-16] The association of migraine and specific vestibular disorders may partially explain the prominent female superiority among vertigo patients because migraine is more common in women.[17] In the vertigo study conducted by Narita et al. with 242 patients, there was a 66% female sex dominance.[18] In our study, there were more female patients among the patients who presented with symptoms of vertigo; this is compatible with the literature. It has been reported that the CV rate increases with age.[19] In our study, no significant difference was found between the patients in terms of sex. However, the median age of the patients with CV was significantly higher than that of patients with PV.

In terms of CV, chronic diseases such as AF, HT, DM, CAD, hyperlipidemia, and cancer are seen as risk factors.[20] It is emphasized that CV should be excluded in patients presenting with vertigo who have risk factors. The concomitant occurrence of hypertension and diabetes mellitus has been correlated with a 4.9-fold escalation in the risk of stroke, as documented in the literature.[21] In our study, the frequency of HT and CAD was statistically significantly higher in patients with CV than in patients with PV.

Autonomic symptoms such as nausea and vomiting are generally more severe and evident in PV attacks than in central-induced vertigo conditions.[22-24] Our study showed that the frequency of nausea, vomiting, and nystagmus was statistically significantly higher in patients with PV, which is in agreement with the literature. Neurologic symptoms such as weakness, dysarthria, vision or hearing changes, paresthesia, altered consciousness, ataxia, or other sensory and motor function changes support the presence of a central cause of vertigo cerebrovascular disease, neoplasm, or multiple sclerosis.[25] In our study, the frequency of hemiplegia, hemiparesis, speech disorder, facial asymmetry, and tinnitus was found to be significantly higher in patients with CV.

In addition to being suitable for use as a prognostic factor in many diseases, a high NLR has been associated with short-term mortality in intracerebral hemorrhages and 3-month mortality.[26] In a study of 123 patients with intracerebral hemorrhage, Wang et al. showed that NLR was independently associated with early hematoma enlargement.[27] In cerebral hemorrhage that may cause CV symptoms, reported N/LR increase supports our study.

Several studies have reported elevated NLR levels in patients with PV. However, these studies typically compared PV patients to healthy adults. In contrast, our study individually evaluated patients with vertigo symptoms at the emergency department. In this regard, we contend that our study employs a methodology more conducive to clinical practice.

In conclusion, we think that NLR is an applicable parameter in distinguishing dizziness due to peripheral or central vertigo in patients presenting with dizziness to emergency departments. A high NLR means that dizziness is caused by central vertigo. Therefore, it supports the need for neurologic imaging as an advanced examination in these patients.

Ethics Committee Approval: Our study was approved by the Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 31.05.2019, decision no: 24237859-439). During the study, the Helsinki Declaration criteria were complied with to protect the patient's data.

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

Author Contributions: Concept-İS, MÇ; Supervision-AG, MY, MÇ, SY; Materials-İS, MÇ, MY; Data Collection and/or Processing-İS, MÇ, SY, AG; Analysis and/or Interpretation-MY, MÇ; Writing-İS, MÇ, SY.

Peer-review: Externally peer-reviewed.

Other Information: This article was produced from a specialization thesis entitled "Acil servise başdönmesi ile başvuran hastalarda periferik ve santral vertigo ayrımında nötrofil/lenfosit oranın tanısal değeri''

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):246-253 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):246-253*

Investigating the Impact of Hibiscus Extracts on Paraoxonase and Antioxidant Activities in Diabetic Rats

Diyabetik Sıçanlarda Hibiskus Ekstraktlarının Paraoxonase ve Antioksidan Aktiviteleri Üzerindeki Etkisinin Araştırılması

[1]Sedef ZIYANOK DEMIRTAS

[1]Bursa Uludag University, Department of Biology, Faculty of Science and Arts, Bursa, Türkiye

Sedef Ziyanok Demirtas: https://orcid.org/0000-0003-3878-3808

ABSTRACT

Objective: Diabetes mellitus (DM) accelerates oxidative stress beyond its broad effects on metabolic function, which has been linked to various chronic complications. This study investigated the antioxidative and therapeutic potential of *Hibiscus syriacus* (HSE) and *Hibiscus trionum* extracts (HTE), focusing on their effects on paraoxonase (PON) and arylesterase enzymes activity in diabetic rat models.

Material and Methods: This study evaluated PON and ARE activities in 36 Wistar albino rats divided into the following groups: control (C), C+HSE, C+HTE, Diabetes (D), D+HSE, and D+HTE. The total phenolic content of HSE and HTE was determined using the Folin- Ciocalteu method, and their antioxidant activities were assessed using DPPH and CUPRAC tests.

Results: HSE and HTE extracts have demonstrated significant increases in paraoxonase and arylesterase activities, which are crucial for cardiovascular protection and reducing oxidative stress in diabetes.

Conclusions: This study highlights the potential of natural extracts in managing oxidative stress-related complications associated with diabetes and underscores the need to integrate such phytotherapeutic agents into broader diabetes care strategies. Future research should focus on confirming these findings in clinical settings and investigating the molecular processes responsible for the observed effects, potentially paving the way for innovative interventions for diabetes management.

Keywords: Antioxidant activity, Diabetes mellitus, *Hibiscus syriacus*, *Hibiscus trionum*, Paraoxonase

ÖZ

Amaç: Diyabetes mellitus (DM), metabolik işlevler üzerindeki geniş etkilerinin ötesinde, çeşitli kronik komplikasyonlarla bağlantılı olan oksidatif stresi hızlandırır. Bu çalışma, diyabetik sıçan modellerinde paraoksonaz (PON) ve arilesteraz enzim aktiviteleri üzerindeki etkilerine odaklanarak *Hibiscus syriacus* (HSE) ve *Hibiscus trionum* ekstraktlarının (HTE) antioksidatif ve terapötik potansiyelini araştırmaktadır.

Materyal ve Metot: Bu çalışma, kontrol (C), C+HSE, C+HTE, Diyabet (D), D+HSE ve D+HTE olmak üzere ayrılan 36 Wistar albino sıçanda PON ve ARE aktivitelerini değerlendirmiştir. HSE ve HTE'nin toplam fenolik içeriği Folin-Ciocalteu metodu ile belirlenmiş, antioksidan aktiviteleri DPPH ve CUPRAC testleri kullanılarak değerlendirilmiştir.

Sonuç: HSE ve HTE ekstraktları, diyabetik kardiyovasküler koruma ve oksidatif stresi azaltmada kritik öneme sahip olan paraoksonaz ve arilesteraz aktivitelerinde önemli artışlar göstermiştir. Sonuç: Bu çalışma, diyabetle ilişkili oksidatif stres komplikasyonlarının yönetiminde doğal ekstraktların potansiyelini vurgulamakta ve bu tür fitoterapötik ajanların geniş kapsamlı diyabet bakım stratejilerine entegre edilmesinin gerekliliğini ortaya koymaktadır. Gelecek çalışmalar, bu sonuçları klinik ortamlarda doğrulamayı ve gözlemlenen etkilerin altında yatan moleküler mekanizmaları araştırmayı hedeflemelidir, bu da diyabet yönetimi için yenilikçi müdahalelerin yolunu açabilir.

Anahtar Kelimeler: Antioksidan aktivite**,** Diyabetes mellitus, *Hibiscus syriacus*, *Hibiscus trionum*, Paraoksonaz

Sorumlu Yazar / Corresponding Author:
Sedef Ziyanok Demirtas,
Department of Biology, Faculty of Science and Arts, Bursa Uludag University, 16059, Bursa, Türkiye
Tel: +905353261970
E-mail: sziyanok@uludag.edu.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 30/04/2024
Kabul Tarihi/ Accepted: 11/07/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Ziyanok Demirtaş S. Investigating the Impact of Hibiscus Extracts on Paraoxonase and Antioxidant Activities in Diabetic Rats. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):246-253. doi: 10.26453/otjhs.1475794

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by consistently high blood glucose levels owing to inadequate insulin production or reduced insulin sensitivity. This can disrupt the metabolism of carbohydrates, fats, and proteins, which may lead to broader health problems. Factors contributing to DM include genetic predispositions, diets high in sugars and fats, obesity, sedentary lifestyles, and oxidative stress that affects lipid metabolism.[1]

Discovered by Abraham Mazur in 1946 the enzyme Paraoxonase (PON1) was further characterized in 1953 by Aldridge W.N. as an A-esterase that breaks down p-nitrophenyl acetate, propionic acid, and butyric acid. Initially, this enzyme was extensively studied in toxicology because of its ability to hydrolyze the organophosphate substrate paraoxon, and thus it was named paraoxonase (EC 3.1.8.1). Later, it was discovered that the enzyme also had an activity that could hydrolyze aromatic esters such as phenyl acetate, which led to it being named arylesterase activity (EC 3.1.1.2). The term "A esterase" was introduced to describe an enzyme capable of hydrolyzing both compounds. However, it was concluded that both paraoxonase and arylesterase activities are characteristic of the PON1 enzyme.[2,3]

For many years, the only recognized function of paraoxonase 1 (PON1) has been to break down organophosphate compounds. However, recent studies have revealed that PON1's physiological role extends to the hydrolysis of lipolactones, which are cyclical esters found in damaged oxidized lipoproteins. Three types of paraoxonases have been identified: PON1, PON2, and PON3, with PON1 being the most thoroughly studied. It is primarily found in the serum. The lipolactonase activity of PON1 plays a crucial role in cardiovascular health by breaking down oxidized lipoproteins that can lead to atherosclerosis. PON1 has been shown to shield lipoproteins from oxidation mediated by free radicals. Additionally, it can break down oxidized cholesterol esters and lipid peroxides.[4]

Studies have shown that PON1 activity is markedly reduced in a broad range of human conditions associated with oxidative stress, including cardiovascular diseases, diabetes mellitus (DM), obesity, renal disease, liver cirrhosis, non-alcoholic steatohepatitis, and various mental disorders.[5]

In DM, it has been observed that PON1 activity decreases, and significant alterations in different blood metabolites also occur.[6] Multiple factors could contribute to the decrease in PON1 activity that has been observed. The lower PON1 activity is thought to be due to the lowering of its specific activity by non-enzymatic glycation because of elevated blood glucose.[7]

Globally, numerous plants with antidiabetic properties are used in traditional medicine for their hypoglycemic, affordable, and antioxidant benefits. These plants support conventional diabetes treatment and offer a holistic management approach. Among these, Hibiscus, from the Malvaceae family, has anti-inflammatory, antidiabetic, and antioxidant properties.[8]

Hibiscus sabdariffa may enhance serum PON1 levels in a dose-dependent manner, potentially mitigating oxidative stress in diabetes. The long-term use of *Hibiscus syriacus* and *Hibiscus trionum* extracts has demonstrated potential antidiabetic, antilipidemic, and hepatoprotective effects in diabetic rat studies. These results highlight the potential of hibiscus and similar antioxidant-rich plants to manage oxidative stress and boost enzyme activities linked to disease resistance.[9,10]

This study aimed to explore the effects of *Hibiscus syriacus* (HS) and *Hibiscus trionum* (HT) extracts on the activities of PON and ARE enzymes in diabetic rats and to evaluate their antioxidative properties to better understand their therapeutic potential.

MATERIALS AND METHODS

The animals used in this study were approved by the Bursa Uludag University Animal Experiments Local Ethics Committee (Date:17.04.2018, decision no: 2018-06/07). All animal studies were conducted in accordance with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) and other guidelines.

Plants and Extraction Methods: Aerial parts of *Hibiscus syriacus* were collected from Kahramanmaraş and *Hibiscus trionum* from Bursa, Türkiye and necrotic sections were discarded. The voucher specimen was deposited at the Herbal Products Laboratory at Bursa Uludağ University with *Hibiscus tyrionum* specific code 45707 and *Hibiscus syriacus* specific code 47614. The plant materials were treated with 30% ethanol for ten minutes to remove contaminants and then washed with tap and distilled water. After air-drying in a shaded area, the samples were ground using a blender. Five grams of this powder were mixed with 50 ml of methanol and repeated three times for consistency. This mixture was then incubated at 40°C for 24 h, centrifuged at 4,500 rpm, and the clear supernatant was extracted using an organic solvent evaporator and stored at +4°C for stability.

Determination of Total Phenolic Content: The total phenolic content of the extract was determined using the Folin-Ciocalteu method, according to Aybastier.[11] Fresh Lowry A, B, and C solutions were prepared using Folin-Ciocalteu reagent diluted 1:3 in

water. Lowry C solution was prepared by combining 50 mL of Lowry A with 1 mL of Lowry B. The assay involved mixing 0.10 mL of the extract, 1.90 mL of water, and 2.50 mL of Lowry C solution, followed by the addition of 0.25 mL of Folin-Ciocalteu reagent. After 30 min, the absorbance was measured at 750 nm using a spectrophotometer. Total phenolic content was reported in mg of gallic acid equivalent (GAE) per g of dry weight (DW) of the plant.

Determination of Antioxidant Capacity:

DPPH Assay: Developed by Brand-Williams et al.,[12] the DPPH assay measures the antioxidant capacity of molecules against the DPPH free radical, a stable molecule with an unpaired electron.[13] In brief, samples were pipetted into 96-well microplates in 100 µL volumes at two-fold dilutions from 2.4 to 10,000 µg/ml. Trolox and ascorbic acid served as reference antioxidants. Each well was treated with 100 µL of DPPH in methanol for a final 0.1 mM concentration. The microplates were incubated at 37 °C for 30 min, and the absorbance was measured at 517 nm using an ELISA microplate reader. The IC50 value, where 50% of the DPPH radicals were neutralized, was derived from the linear progression of the curve. Antioxidant activity was reported in milligram Trolox equivalents per gram of freeze-dried sample.

CUPRAC Assay: Developed by Apak et al.,[14] the CUPRAC method measures the reduction of copper (II) ions by polyphenols in a Cu (II)-neocuproine solution, indicating "Copper Reducing Antioxidant Capacity." Samples were added to 50 µL volumes at two-fold dilutions from 2.4 to 10,000 µg/ml into wells. Freshly prepared CuCl2, NH4Ac, and neocuproine were added in 150 µL volumes. Cu(I)–Nc chelates were spectrophotometrically measured at 450 nm. Antioxidant capacity was expressed in mg Trolox equivalents per gram of lyophilized sample.

Animals: Thirty-six male Wistar rats, weighing 350–400 g, were housed under standard conditions with free access to food and water at a steady temperature of 25 ± 2°C and 55 ± 5% humidity with a 12-hour light-dark cycle. Ethical standards were followed to ensure animal welfare. Rats were administered daily morning doses of *Hibiscus trionum* extract (HTE) and *Hibiscus syriacus* extract (HSE) via gavage.

Induction of Diabetes: Type 1 diabetes was induced in overnight-fasted rats via a single intraperitoneal injection of 65 mg/kg streptozotocin (STZ; Sigma). The control group received a citrate buffer injection. Blood glucose levels were measured two days post-STZ injection, with inclusion in further research requiring levels of 200 mg/dL or higher.

Grouping of animals: Animals were randomly assigned and separated into six different groups as follows:

1.The healthy rats (control group) “C” (n=6),

2.The healthy rats administered with *Hibiscus syriacus* extract “C+HSE” (n=6),

3. The healthy rats administered with *Hibiscus trionum* extract “C+HTE” (n=6),

4.The diabetic rats “D” (n=6),

5.The diabetic rats administered with *Hibiscus syriacus* extract “D+HSE” (n=6),

6.The diabetic rats administered with *Hibiscus trionum* extract “D+HTE (n=6).

The rats in the "C+HSE", "C+HTE", "D+HSE", and "D+HTE" groups received *H. syriacus* and *H. trionum* extracts (100 mg/kg/day) simultaneously over four weeks via gavage. This method involves administering the extracts directly into the stomach through a tube passed down the throat, ensuring precise dosage and absorption. This is important for the accuracy and consistency of the dose used in the study.

Biochemical Analysis Procedures: At the end of the study, after a 12-hour fast, the animals were euthanized via cardiac puncture under anesthesia. Blood was collected in serum-specific tubes, centrifuged at 1500 rpm for 10 min to extract serum, and stored at -20 °C. Kidney and liver tissues were immediately preserved at -20 °C, rinsed with saline, and suspended in 1.15% potassium chloride (KCl). The tissues were homogenized using a T-line laboratory mixer (model No: 136-2), then centrifuged at 3000 rpm for 15 minutes at +4 °C. The supernatant was used for further analyses.

Serum Paraoxonase Activity: To assess PON activity, 15.62 µL of serum was combined with 2.5 mL of a solution containing 1.0 mM paraoxon, 1.0 mM CaCl2, and 0.05 M glycine-sodium hydroxide buffer at pH 10.5. PON's release of p-nitrophenol from paraoxon at 25 °C was measured at 412 nm using a spectrophotometer. The spontaneous non-enzymatic hydrolysis rates from the blank control were subtracted to determine the true absorbance. PON activity was defined as the production of 1 µmol p-nitrophenol per minute, reported as units per liter (U/L).[15]

Serum Arylesterase Activity: The enzyme activity of serum PON1 arylesterase was measured by the hydrolysis of phenylacetate into phenol and acetate, with the absorbance of phenol at 270 nm indicating the arylesterase activity. A substrate solution of 20 mM Tris-HCl buffer (pH 8.00), 1 mM CaCl2, and 1 mM phenylacetate was prepared immediately before use. Measurements were conducted at 25°C using a 270 nm wavelength over 2 min against a blank. The change in absorbance was recorded, and enzyme activity was calculated from this change and expressed in units per liter (U/L).[15]

Statistical Analysis: Statistical evaluations were conducted using SPSS (version 28.0) for Windows, with data presented as mean ± Standard Error. Fol-

lowing normality test outcomes, the Kruskal-Wallis non-parametric test was used for analysis. Differences between groups were assessed using Tamhane's T2 test for post hoc comparisons, with a significance threshold set at $p \leq 0.05$.

RESULTS

The total phenolic content of the Hibiscus species, expressed in milligrams of gallic acid equivalent per gram of dried weight, was determined using the Folin-Ciocalteu method and is presented in Table 1. The total phenolic contents in *Hibiscus syriacus* and *H. trionum* were 7.79 ± 0.06 and 7.22 ± 0.13 mg GAE/g, respectively. The total phenolic content was slightly higher in the HSE than in HTE.

The DPPH assay results of Hibiscus species are shown in Figure 1A. An absorbance/concentration graph was plotted, and the values where a linear increase occurred were determined first. According to the curve equation created from these values, the concentration at which the extract scavenges half of the DPPH free radicals (IC50) was calculated.

These antioxidant activities were quantified using Trolox-equivalent antioxidant capacity (TEAC) values, HSE IC50: 973 ug/ml, HTE IC50: 886 ug/ml and Trolox IC50: 3,7 ug/ml. Both Hibiscus species showed low DPPH scavenging activity. Compared to Trolox (3,7 ug /ml), statistically non-significant results were obtained in terms of the IC50 value of DPPH free radical scavenging activity between both HSE and HTE extracts (Figure 1A). The CUPRAC assay results of Hibiscus species are shown in Figure 1B. An absorbance/concentration graph was plotted, and the values where a linear increase occurred were determined first. A curve equation was developed based on these values. The absorbance value corresponding to a 1 mg/ml solution containing Trolox was calculated, and the corresponding plant extract solution concentrations required to obtain this value were determined using the respective curve equations. Thus, the CUPRAC antioxidant capacity was determined as the activity of the extract solution corresponding to the activity of 1 µg Trolox, expressed in µg (µg Trolox equivalents/µg extract).

The antioxidant capacities were measured and expressed in terms of Trolox-equivalent antioxidant capacity (TEAC) values. HSE Trolox eq: 14.13 mg Teq /g dry weight HS and HTE Trolox eq: 21.29 mg Teq /g dry weight HT and Trolox eq: 59.60 ug/ml (Figure 1B).

Table 1. The total phenolic content of *H. syriacus* and *H. trionum* extracts.

Extracts	Total Phenolic Content mg/gallic acid/g plant
H. syriacus extract (HSE)	7.79±0.06
H. trionum extract (HTE)	7.22±0.13

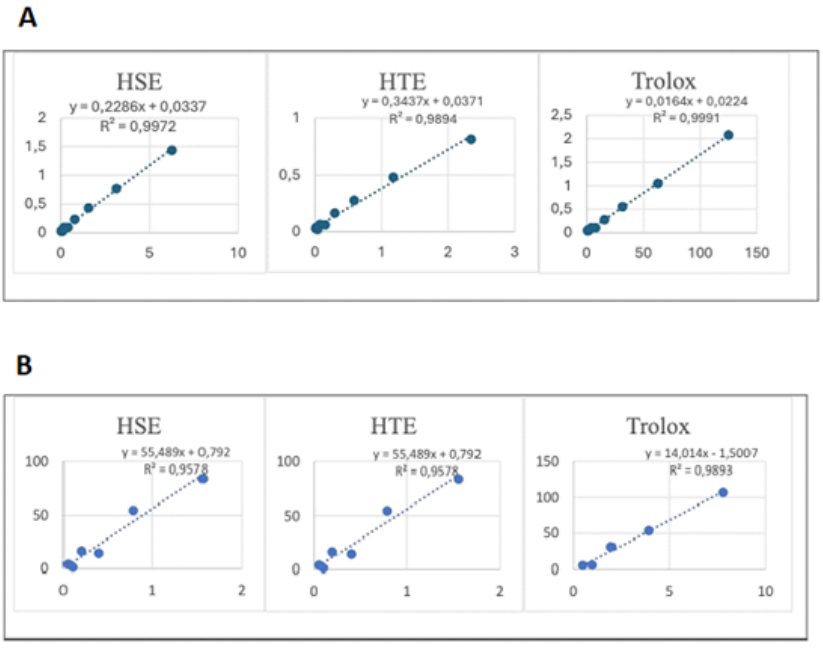

Figure 1. The DPPH (A) and CUPRAC (B) assay results of Hibiscus species. HSE: *Hibiscus syriacus* extract; HTE: *Hibiscus trionum* extract.

Comparisons of the antioxidant activity of *H. syriacus* and *H. trionum* species from different tests are shown in Figure 2.

The PON activities of diabetic and healthy rats treated with *H. syriacus* and *H. trionum* extracts in the serum, liver, and kidney tissues are shown in Table 2. Both serum and tissue (liver, kidney) PON activity were significantly lower in the diabetic group versus the control group ($p < 0.05$, 0.01). Both *Hibiscus syriacus* extract (HSE) and *Hibiscus trionum* extract (HTE) caused significantly increased PON activities in the C + HSE, C + HTE, D + HSE, and D + HTE groups compared to the C and D groups (Respectively, $p < 0.05$, 0.01; Table 2).

The arylesterase activities of diabetic and healthy rats treated with *H. syriacus* and *H. trionum* extracts in the serum are shown in Figure 3. ARE activity was notably reduced in the diabetic group (58 U/L) compared to the control group (154 U/L) ($p < 0.05$, 0.01). *Hibiscus syriacus* extract (HSE) and *Hibiscus trionum* extract (HTE) significantly enhanced ARE activities in the C + HSE (185 U/L), C + HTE (220 U/L), D + HSE (121 U/L), and D + THE (138 U/L) groups relative to the C and D groups, respectively ($p < 0.05$, 0.01).

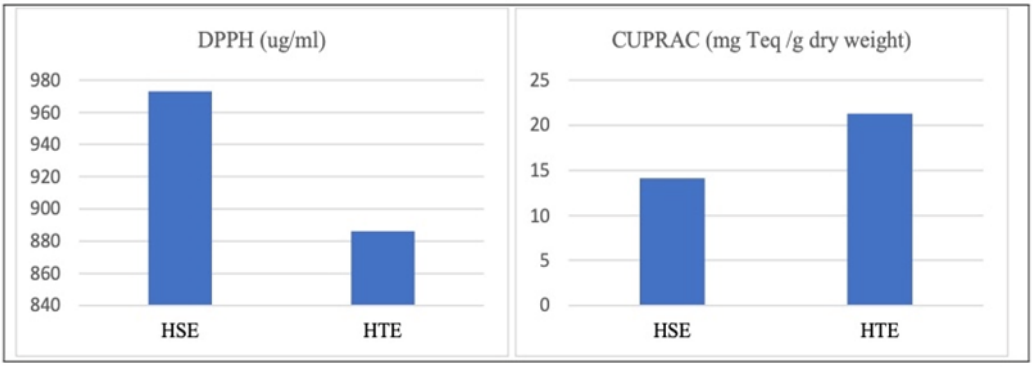

Figure 2. The antioxidant activity of *Hibiscus syriacus* and *Hibiscus trionum* species.

Table 2. The PON Activities in Diabetic and Healthy Rats Treated with *H. syriacus* and *H. trionum* Extracts.

Extracts	PON Activity		
	Serum (U/L)	Liver (U/g/tissue)	Kidney (U/g/tissue)
C	120±1	80±1	35±2
C +HSE	142±2 ^{a*}	92±1	41±2
C +HTE	162±4 ^{a*}	108±2 ^{a*}	56±2 ^{a*}
D	48±1 ^{a**}	41±1 ^{a*}	22±1 ^{a*}
D + HSE	116±2 ^{b*}	61±2	30±2
D + HTE	118±3 ^{b*}	78±3 ^{b*}	33±2 ^{b*}

a: Compared with control. b: Compared with diabetes group. Statistical significance: *p<0.05, **p< 0.01; PON: Paraoxonase; C: Control; C +HSE: Control + *Hibiscus syriacus* extract; C +HTE: Control + *Hibiscus trionum* extract; D: Diabetes; D+HSE: Diabetes + *Hibiscus syriacus* extract; D+HTE: Diabetes + *Hibiscus trionum* extract.

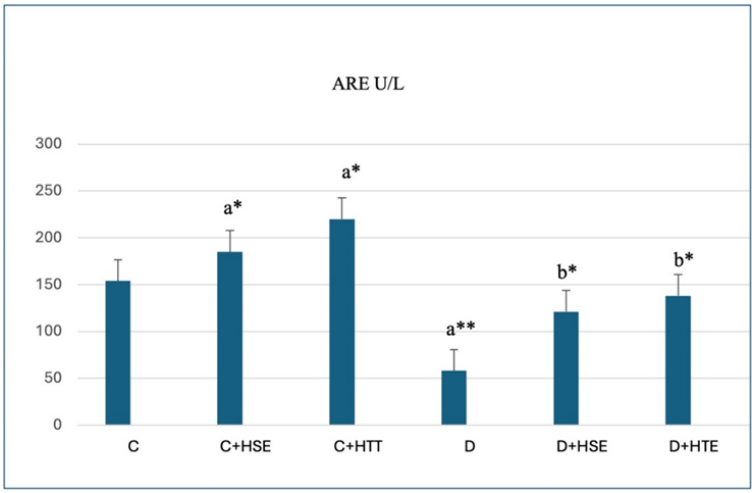

Figure 3. The arylesterase enzyme activities in control and experimental groups of rats treated with *H. syriacus* and *H. trionum* extracts. ^{a}: Compared with control; ^{b}: Compared with diabetes group. Statistical significance: *: p<0.05, **: p< 0.01. ARE: Arylesterase; C: Control; C +HSE: Control + *Hibiscus syriacus* extract; C +HTE: Control + *Hibiscus trionum* extract; D: Diabetes; D+HSE: Diabetes + *Hibiscus syriacus* extract; D+HTE: Diabetes + *Hibiscus trionum* extract.

DISCUSSION AND CONCLUSION

Historically, natural products have served therapeutic and preventive roles in the treatment of diseases, such as diabetes. Over time, these drugs have evolved into specific medications; however, today, synthetic drugs are often replaced. Despite this, interest in herbal treatments remains strong, especially in East and Southeast Asia and other regions with diverse flora, where natural remedies are considered viable diabetes treatments. Research indicates that natural products generally have fewer side effects than synthetic drugs, promoting their use in the management of chronic diseases. Moreover, their use to reduce the side effects of conventional diabetes medications has gained popularity.[16]

Despite their popularity, the lack of precise dosage and usage studies of plants and herbal products can result in reliability issues and adverse outcomes. In phytotherapy, metabolites, such as phenolics and flavonoids, which are crucial in fighting diabetes, are well studied for their high antioxidant levels and effectiveness against oxidative stress, providing protective benefits against bodily damage.[17]

The DPPH assay, a method that uses a stable free radical soluble in methanol or ethanol, changes color upon neutralization by antioxidants. Substances are categorized based on their antioxidant strength, with IC50 or EC50 values below 50 µg/ml considered very strong antioxidants, between 50-100 µg/ml strong, 101-150 µg/ml moderate, and above 150 µg/ml weak.[18]

The CUPRAC method detects hydroxyl radicals (OH) and measures OH scavenger activity. The hydroxyl radical, the most reactive of all reactive oxygen species (ROS), exhibits significant reactivity. In this assay, a sample is considered to have antioxidant capabilities if it can reduce Cu (II) to Cu (I), indicating a strong reduction potential.[14] In the present study, in the antioxidant activity tests comparing the two methods, the DPPH method displayed weaker antioxidant activity with a higher IC50 value, highlighting a significant difference compared with the CUPRAC method. CUPRAC exhibited the highest antioxidant activity of Hibiscus species (Fig 1-2). The antioxidant capacity of plants is often associated with the presence of phenolic compounds and flavonoids. Phenolic compounds are known to possess antioxidant effects owing to their oxidation-inhibiting properties. These compounds function as reducing agents, hydrogen donors, singlet oxygen quenchers, and chelators. Flavonoids neutralize free radicals by donating hydrogen atoms, thereby acting as antioxidants.

Despite their popularity, imprecise dosing and usage guidelines for plants and herbal products can lead to reliability concerns and negative effects. In phytotherapy, key metabolites such as phenolics and flavonoids, which are essential for combating diabetes, are noted for their strong antioxidant properties and efficacy against oxidative stress, offering protection against bodily damage.[19]

PON enzyme activity is linked with various diseases, including inflammation, stroke, myocardial infarction, obesity, hypercholesterolemia, renal failure, hypertension, diabetes, and Alzheimer's disease. Reduced PON activity has been identified as a cause of inflammation, particularly in cancer and diabetes patients. Studies indicate that expressing human PON1 in mice prevents diabetes by enhancing its antioxidant properties and promoting insulin secretion from pancreatic β-cells.[20,21]

This study found that the administration of hibiscus extracts to diabetic rats improved PON1 and ARE activity. Our research has observed a reduction in PON activity within the diabetic group; in the diabetic groups, treatment with HSE and HTE led to significant increases in paraoxonase activity; overall activity increased by 109% and 137%, liver activity by 48% and 99%, and kidney activity by 36% and 50%, respectively (Table 2). In the control groups receiving HSE and HTE, arylesterase activity increased by 20% and 43%, respectively, whereas in the diabetic groups receiving HS and HT, the increase was 109% and 137%, respectively (Fig. 4). In this decrease of the diabetic group is thought to be associated with hyperglycemia and oxidative stress. Treatment led to significant increases in paraoxonase and arylesterase activities in both healthy and diabetic groups, suggesting beneficial effects on metabolic functions. The decrease in PON activity in diabetic groups is thought to be associated with hyperglycemia and oxidative stress.

These findings align with those of Bahlil et al.,[22] who reported increased PON1 levels in hypercholesterolemic diabetic rats supplemented with *Zygophyllum album*. PON1, an enzyme associated with HDL, possesses antioxidant and anti-inflammatory properties that can mitigate the oxidation of atherogenic LDL, offering protection against it.[23] The significant increase in PON1 activity could be a result of enhanced synthesis and/or secretion of HDL-C.

This research confirms that plant-based antioxidants can effectively modulate PON1 activity, as supported by strong evidence from animal models. According to the results of this study, *H. trionum* is more effective than *H. syriacus* in terms of antioxidative activity and treatment of complications caused by diabetes. This can be explained by the presence of different and more effective bioactive molecules in *H. trionum* than in *H. syriacus.* However, the variability in antioxidant effects due to environmental factors calls for further methodological research, especially to verify the impacts of *Hibiscus syriacus* and *Hibiscus trionum* at physiological doses. This

study highlights the necessity of using FDA-recommended doses in clinical trials to maximize benefits while ensuring safety. Future research is needed to explore the metabolic effects of polyphenols on human health, emphasizing the importance of natural antioxidants in clinical settings and their regulatory compliance.

In conclusion, ongoing exploration of the role of natural antioxidants in clinical applications is crucial. It not only helps to refine our understanding of their therapeutic potential but also ensures that the interventions are both effective and safe, aligning with regulatory standards, and addressing the variability introduced by biological and environmental factors.

Ethics Committee Approval: Our study was approved by the Bursa Uludag University Animal Experiments Local Ethics Committee (2018-06/07).

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

Author Contributions: Concept – SZD; Supervision – SZD; Materials – SZD; Data Collection and/or Processing – SZD; Analysis and/or Interpretation – SZD; Writing – SZD.

Peer-review: Externally peer-reviewed.

Financial Support: This study was supported by a Bursa Uludag University grant OAP(F)-2018/11.

Acknowledgements: I would like to express our gratitude to Ahmet ILCIM for his contribution to plant identification. I will be forever grateful and extend my heartfelt thanks to the late Prof. Dr. Hulusi MALYER, who made highly appreciated contributions to the identification of the Hibiscus plant and very sadly passed away due to COVID-19. I extend my utmost thanks to Prof. Dr. Serap CELİKLER for her valuable support.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):254-262 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):254-262*

Propofol's Neuroprotective Effect Against Cisplatin-Induced Oxidative Neurotoxicity Via Suppression of the TRPM2 Cation Channel

Propofol'ün, TRPM2 Katyon Kanalını Bastırarak Sisplatin Kaynaklı Oksidatif Nörotoksisiteye Karşı Nöroprotektif Etkisi

[1]Haci Ömer OSMANLIOĞLU

[1]Department of Anesthesiology and Reanimation, School of Medicine, Suleyman Demirel University, Isparta, Türkiye

Haci Ömer Osmanlıoğlu https://orcid.org/0000-0002-8622-6072

ABSTRACT

Objective: Cisplatin (CSP) exhibits strong oxidant and apoptotic effects in tumors, but it also causes adverse neurodegenerative effects by stimulating the TRPM2 cation channel. By regulating mitochondrial reactive free oxygen species (ROS) and excessive Ca^{2+} entry-mediated apoptosis, propofol (PRPF) exhibits antioxidant and neuroprotective properties. However, the action of the TRPM2 in these productions in human SH-SY5Y neuronal cells has not yet been determined. In SH-SY5Y, I investigated the protective effects of PRPF by modifying TRPM2, which affects CSP-induced neuronal mitochondrial function and death.

Materials and Methods: I generated five main groups in the SH-SY5Y as control, PRPF (200 μM for 24h), CSP (25 μM for 24h), CSP + PRPF, and CSP + TRPM2 channel antagonists (25 μM ACA and 100 μM 2APB).

Results: Through TRPM2 stimulation, the incubation with CSP increased the amounts of apoptosis, caspase -3, caspase -9, cell death percentage, ROS, mitochondrial hyperpolarization, TRPM2 current densities, and intracellular free Ca^{2+}. However, the incubation of PRPF through the inhibition of TRPM2 decreased the amounts of these processes.

Conclusions: PRPF treatment via TRPM2 suppression decreased the levels of mitochondrial oxidative stress and neuronal death caused by CSP. One effective therapy option for CSP-induced mitochondrial oxidative neuronal damage is the PRPF.

Keywords: Cisplatin, neuronal injury, oxidative stress, propofol, TRPM2 channel

ÖZ

Amaç: Sisplatin (CPS), TRPM2 kanalını aktive ederek tümör hücrelerinde oksidan ve apoptotik etki meydana getirmesine rağmen bu etkilerin sinir hücrelerindeki yan etkilerinden dolayı CSP kullanımını sınırlandırmaktadır. Propofol (PRPF) mitokondriyal reaktif oksijen türleri (ROS) ve aşırı Ca^{+2} girişine bağlı apoptozisi düzenleyerek antioksidan ve nöroprotektif etki göstermektedir. Bununla birlikte, PRPF'un TRPM2 kanalını düzenleyerek antioksidan ve anti-apoptotik etki meydana getirebileceği insan SH-SY5Y sinir hücrelerinde henüz araştırılmamıştır. Bu çalışmanın amacı PRPF tedavisinin TRPM2 kanalını düzenleyerek sinir hücre ölüm ve mitokondriyal ROS üretimi üzerindeki etkilerinin SH-SY5Y hücrelerinde araştırılmasıdır.

Materyal ve Metot: SH-SY5Y hücrelerinde 5 ana grup oluşturulmuştur. Bu gruplar: Kontrol, PRPF (200 μM ve 24 saat), CSP (25 μM ve 24 saat), CSP + PRPF ve CSP + TRPM2 kanal blokörleri (25 μM ACA ve 100 μM 2APB).

Bulgular: CSP inkübasyonu, TRPM2 kanalını uyararak apoptosis, kaspaz -3, kaspaz -9, hücre ölümü yüzdesi, ROS, mitokondriyal hiperpolarizasyon, TRPM2 akım yoğunlukları ve hücre içi Ca^{+2} miktarı artırdı fakat hücre canlılığını azalttı. Bununla birlikte, PRPF, ACA ve 2APB tedavileri sonraları bu değerler normal değerlerine döndüler.

Sonuç: PRPF tedavisi TRPM2 kanalı inhibe ederek CSP neden olduğu mitokondriyal oksidan ve apoptotik etkileri azalttı. PRPF tedavisi, CSP neden olduğu mitokondriyal oksidatif stres ve sinir hücre harabiyetini önlemede potansiyel kaynak olarak gözükmektedir.

Anahtar Kelimeler: Oksidatif stres, propofol, sinir hasarı, sisplatin, TRPM2 kanalı

Sorumlu Yazar / Corresponding Author:
Haci Ömer Osmanlioğlu,
Department of Anesthesiology and Reanimation, Faculty of Medicine, Suleyman Demirel University, Isparta, Türkiye
Tel: +905055142946
E-mail: omerosmanlioglu@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 12/08/2024
Kabul Tarihi/ Accepted: 02/09/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Osmanlıoğlu HÖ. Propofol's Neuroprotective Effect Against Cisplatin-Induced Oxidative Neurotoxicity Via Suppression of the TRPM2 Cation Channel. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):254-262. doi: 10.26453/otjhs.1532340

INTRODUCTION

Numerous physiological and pathological circumstances can produce excessive reactive free oxygen species (ROS).[1,2] Some Ca^{2+} permeable cation channels were stimulated by the ROS, resulting in neuron injury. TRP melastatin 2 (TRPM2) is a member of the transient receptor potential (TRP) class.[3,4] While non-specific antagonists such 2-aminoethoxydiphenyl borate (2APB) and N-(p-amylcinnamoyl) anthranilic acid (ACA) decrease TRPM2 activation, oxidants (such as H_2O_2) and ADP-ribose (ADPR) enhance it.[2,5] Recently, it was shown that ACA and 2APB modulate apoptosis and ROS in neuronal cells, including SH-SY5Y cells, by inhibiting TRPM2.[6,7] Through the simulation of caspase -3 and -9, TRPM2 stimulation causes mitochondrial oxidative neurotoxicity and apoptosis, although antioxidant therapy that inhibited it reduced the oxidative and apoptotic activities via the inhibition of TRPM2 in human SH-SY5Y neuronal cells and mouse dorsal root ganglion (DRG).[6,7]

Cisplatin (CSP) is used to treat solid tumors and malignancies. However, significant side effects of CSP, namely oxidative neurotoxicity and apoptosis, restrict its chemotherapeutic potential and cause a decline in the use of CSP.[8,9] Moreover, anticancer medications cause the generation of ROS, which reduce the antioxidant activity of CSP without TRPM2 activation,[10] but glioblastoma tumor cells are killed by CSP-mediated TRPM2 stimulation and ROS.[11] According to recent studies, TRPM2-channel stimulation-induced apoptosis and ROS are highly correlated with increases in CSP-induced nephrotoxicity and optic nerve damage.[12-14]

Propofol (PRPF) is a commonly utilized intravenous sedative-hypnotic drug that is used for anesthesia and sedation.[15] The antioxidant structure of PRPF exhibits similarities to the structure of vitamin E due to the presence of a phenolic hydroxyl group.[8,15] Studies on mouse hippocampus neurons and SH-SY5Y cell lines have shown that PRPF has anti-apoptotic and antioxidant properties.[8,15] By inhibiting the receptor (N-methyl-D-aspartic acid, NMDA) stimulation-caused Ca^{2+} influx in rodent brain, PRPF also reduced oxidative stress.[16-18] According to findings, PRPF inhibited TRP ankyrin 1 (TRPA1) and TRP vanilloid 1 (TRPV1)-mediated in rats to promote cardioprotection.[20,21] In contrast to previous results, PRPF enhanced pain sensitivity by activating the TRPV1 channel in the mouse and human DRGs.[21,22]

To my knowledge, no research has been done on how CSP stimulates TRPM2 in SH-SY5Y neuronal cells to cause oxidative neurotoxicity and apoptosis. Therefore, the purpose of the current investigation was to assess the impact of PRPF on CSP-induced mitochondrial oxidative damage and apoptosis using SH-SY5Y.

MATERIALS AND METHODS

Ethics Committee Approval: The study was approved by the ethics committee and used cells that were grown using commercially available cell culture. This study doesn't need to have ethics committee approval.

Cells: For CSP and PRPF studies, a significant number of SH-SY5Y cells was used.[14,16] According to the results of a recent study,[4] SH-SY5Y cells naturally expressed TRPM2. Two reasons led to the use of SH-SY5Y (ATCC, VA, USA) in the current investigation. The SH-SY5Y was grown in a cell culture environment, as described in previous studies.[4,14] Ten percent fetal bovine serum, 1% antibiotic mixture, and 90% DMEM/Ham's F12 equal mixture made up the medium combination.[4,27]

Experimental Groups: Five 25 cm^2 sterile flasks containing $1x10^6$ SH-SY5Y cells were utilized for the five groups: control (CNT), PRPF, CSP, CSP + PRPF, and CSP + ACA or CSP + 2APB. For twenty -four hours, the SH-SY5Ys of the CNT were kept in the incubator. The cells in the PRPF and CSP + PRPF groups were treated with 200 uM of PRPF, and they were then incubated for a full day.[23] For a whole day, the cells of the CSP received CSP (25 μM).[11,14] The cells of CSP + ACA and CSP + 2APB groups were one hour incubated with 25 μM ACA and 100 μM 2APB after the 25 μM CSP (24h) incubation.[4]

The SH-SY5Y were cultured in Mattek Corporation bottom-glass plates (Ashland, MA, USA) in order to conduct research using an Axio Observer for laser confocal microscopy (LSM-800). Plan-Apochromat 40x1.3 oil objective with Z1/7 microscope (Zeiss, Oberkochen, Germany). In order to prepare for the plate reader and electrophysiology investigations, the cells were grown in sterile flasks.

The Determination of Free Intracellular Ca^{2+} ($[Ca^{2+}]_i$) Amount: To find out how CSP and PRPF affected the $Ca^{2+}]_i$ amount in the cells, I stained the SH-SY5Y by using a fluorescent dye (Fluo 3⁄AM, Cat # F1242, Invitrogen, Istanbul, Türkiye), and they were analyzed in the LSM-800 confocal microscope.[4,6] The TRPM2 channel was blocked by 100 μM 2APB, whereas H_2O_2 (1 mM) activated it. The fluorescence intensity variability was expressed in arbitrary units (a.u.).

Electrophysiology: Using a HEKA EPC-10 double amplifier (Lamprecht, Germany) and a room-temperature patch clamp, conventional electrophysiological measurements (whole-cell) were performed.[3] The components of the intracellular (patch pipette) and extracellular (patch chamber) solutions

were identified by earlier studies.[3,4,5] To produce the Na^+-free extracellular solution, 150 mM Ca^{2+} chelator (N-methyl-D-glucamine, $NMDG^+$) was added. The voltage of cells was adjusted to -60 mV. To lower the intracellular (1 mM ADPR)-generated TRPM2 currents in cells, the study used an extracellular (25 μM ACA) TRPM2 antagonist. As pA/pF, the TRPM2 current findings were shown.

Assays for Caspase-3, -9, Apoptosis, and Cell Viability: Using an automated Infinite PRO 200 microplate reader of Tecan GmbH (Groedig, Austria), the changes in cell viability (MTT) absorbance were evaluated at 490 and 650 nm. An APOPercentage commercial kit (Biocolor Ltd., Co Antrim, UK) was used to assess SH-SY5Y apoptosis. Changes in apoptosis in absorbance at 550 nm were detected using the plate reader (Infinite PRO200). Apoptosis occurs when Ac-DEVD-AMC, a protease substrate of caspase-3, is activated. Moreover, Ac-LEHD-AMC is a fluorogenic substrate of caspase-9. The substrate cleavages at 380–460 were assessed using the Infinite PRO 200 plate reader following obtaining the two substrates from Bachem AG (Bubendorf, Switzerland).

Analysis of Cell Death: In the cell culture conditions, Hoechst 33342 (9 μM) and PI (2 μM) were incubated in the incubator. The LSM-800 was equipped with an inverted microscope (Axio Observer.Z1/7, Zeiss) and an objective (Plan-Apochromat 40x/1.3 Oil DIC-UV) in order to take images of red PI-positive (death) SH-SY5Y and blue live Hoechst 33342. Black and white bright field (BF) pictures of the cells were taken by the Axiocam 702 camera.[4]

Assays for the Production of ROS: For measuring the quantity of ROS in the LSM-800, the ROS probe (DCFH-DA) (Cat # D399, Thermo Fisher Sci.) was used.[24] The ROS studies used the 504 nm excitation and 525 nm emission wavelengths, whereas the green DCFH-DA records kept the argon laser stimulation wavelength at 488 nm.[4]

The Assessment of the Hyperpolarization of the Mitochondrial Membrane (mHP): A cationic carbocyanine dye called JC-1 accumulates in mitochondria. When membrane potentials are hyperpolarized in living cells, the JC-1 probe manifests as an orange -fluorescent J-aggregate and appears as a green-fluorescent monomer, as described by the manufacturer (Thermo Fischer Scientific).[14] The JC-1 fluorescence was also measured with the LSM-800. The laser stimulation wavelengths (488 nm) of LSM-800 were used in the orange JC-1 records, whereas the 593 nm excitation and 595 emission wavelengths were used for recording the images.

Statistical Assays: I presented the results using the mean and standard deviation (SD). The statistical significance was assessed using variance, also known as ANOVA, using the SPSS software (25.0). To determine the statistical significance, a p-value of less than $p < 0.05$ was used.

RESULTS

While Figure 1A shows the green pictures of the fluorescent dye in four groups (CNT, PRPF, CSP, and CSP + PRPF), Figures 1B and 1C show the mean fluorescence intensities as a result of H_2O_2 stimulation and 2APB inhibition, respectively. Compared to the CNT and PRPF, the CSP had greater ($p < 0.05$) variations in Fluo 3/AM intensity (Figure 1B). However, the changes were less noticeable in the CSP + PRPF compared to the CSP alone ($p < 0.05$). As a result, I observed that by activating TRPM2, applying PRPF to SH-SY5Y decreased the CSP-mediated rise of $[Ca^{2+}]_i$ amount.

When SH-SY5Y was not stimulated by ADPR (Figure 2A), the TRPM2 current of cells did not alter. On the other hand, TRPM2 was activated by ADPR (1 mM) stimulation [Figs. 2B and 2B (I-V)]. The pA/pF values of TRPM2 in the cells were greater in the CNT plus ADPR compared to the CNT (Figure 2F) ($p < 0.05$). The pA/pF values of TRPM2 in the cells were further ($p < 0.05$) increased in the CSP plus ADPR by stimulating ADPR [Figures 2C and 2C (I-V)]. In comparison to CSP plus ADPR and CNT plus ADPR, the pA/pF value of TRPM2 in the cells was considerably ($p < 0.05$) lower in the CSP plus ADPR plus ACA and CNT plus ADPR plus ACA (Figure 2F). TRPM2 currents did not increase after ADPR stimulation by treatment PRPF (Figure 2D) or CSP plus PRPF (Figure 2E). The pA/pF values of TRPM2 currents in the cells were considerably ($p < 0.05$) lower in the PRPF and CSP plus PRPF groups than in the CSP plus ADPR group.

Cell viability (Figure 3A) decreased ($p < 0.05$) in the CSP compared to the CNT and PRPF but increased ($p < 0.05$) in the CSP plus PRPF and CSP plus ACA. Apoptosis (Figure 3B), caspase -3 (Figure 3C), and caspase -9 (Figure 3D) activity were also elevated in the CSP, although they were decreased in the CSP plus PRPF and CSP plus ACA groups by the treatment of PRPF and ACA ($p < 0.05$).

BF, PI (red), Hoechst 33342 (blue), and their overlay and 2.5D merge images were indicated in the Figure 4A. The PI positive SH-SY5Y percentage in the CSP was greater ($p < 0.05$) in the PI/Hoechst pictures than in the CNT and PRPF; however, the percentages in the CSP plus PRPF and CSP plus ACA groups were lower ($p < 0.05$) than in the CSP group alone (Figure 4B).

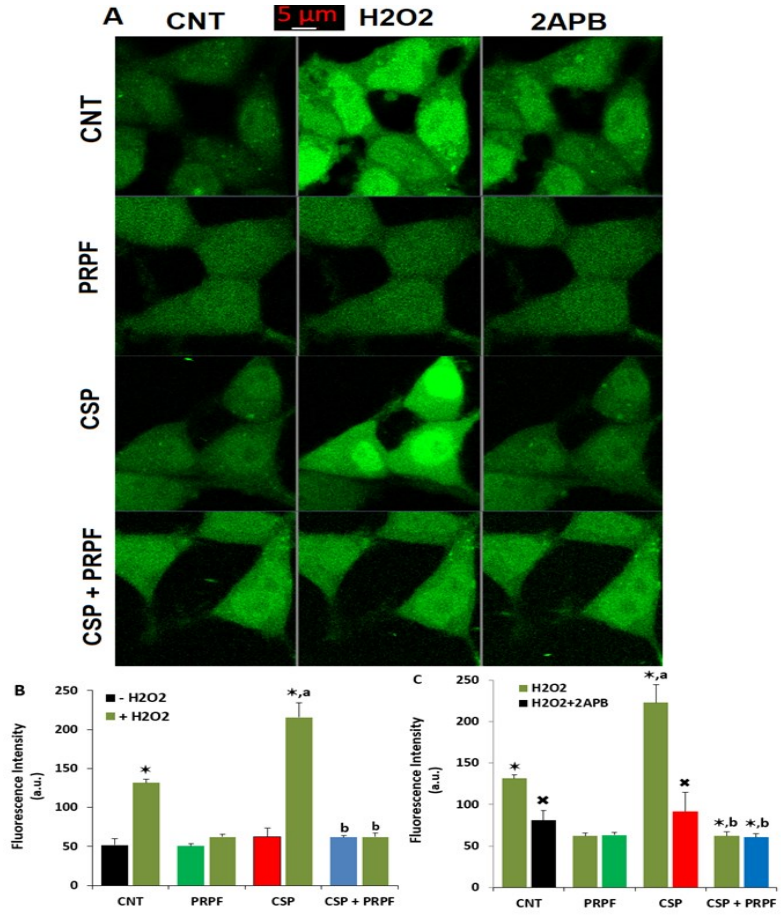

Figure 1. The incubation of propofol (200 µM) modulated cisplatin (25 mM ACA)-caused the increase of $[Ca^{2+}]_i$ in the SH-SY5Y cells. (Mean ± SD); For TRPM2 stimulation, 1 mM H_2O_2 was used, although 100 uM 2APB used for the TRPM2 inhibition; **A**: The Fluo 3/AM typical images; **B:** CNT and CNT + H_2O_2 **C**. CNT + H_2O_2 and CNT + H_2O_2 +2APB; Arbitrary unit: a.u; Scale bar: 5 µm. ([a]$p < 0.05$ versus (vrs.) CNT and PRPF; [b]: $p < 0.05$ vrs. CSP; [ē]: $p < 0.05$ vrs. (- H_2O_2 group); [O]: $p < 0.05$ vrs. (+ H_2O_2 group).

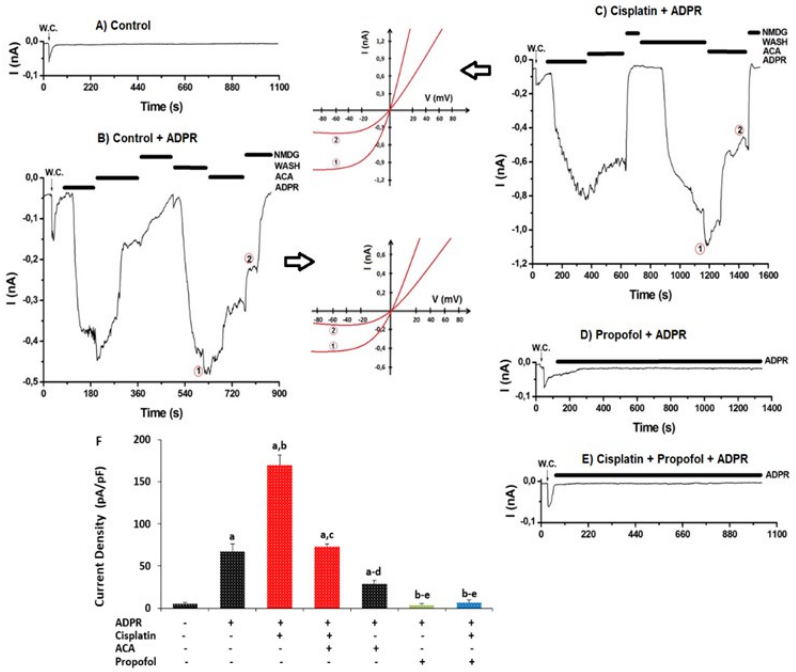

Figure 2. Treatments of propofol (200 µM for 24h) reduced the cisplatin (25 µM for 24h)-mediated TRPM2 pA/pF values. (n = 4 and mean ± SD); The pA/pF values of TRPM2 were induced when 1 mM ADPR was given intracellularly to the cells using a patch pipette; however, these currents were blocked by 25 uM ACA and $NMDG^+$; The whole cell: W.C.; A: Control; B: Control plus ADPR; C: ADPR with cisplatin; D: Propofol; E: Cisplatin plus Propofol plus ADPR; F: The average TRPM2 current densities. The voltage ramps caused by ADPR and ACA in the cells shown in Figs. 3B and 3C, respectively, were denoted by the numbers 1 and 2; The corresponding I-V relationships from Figs. 3B and 3C were displayed in Figs. 3B-I/V and 3C-I/V. ([a:] $p < 0.05$ *vrs*. Control; [b]: $p < 0.05$ *vrs.* control plus ADPR; [c]: $p < 0.05$ *vrs.* cisplatin plus ADPR; [d]: $p < 0.05$ *vrs.* cisplatin plus ADPR plus ACA; [e:] $p < 0.05$ *vrs.* Control+ADPR+ACA).

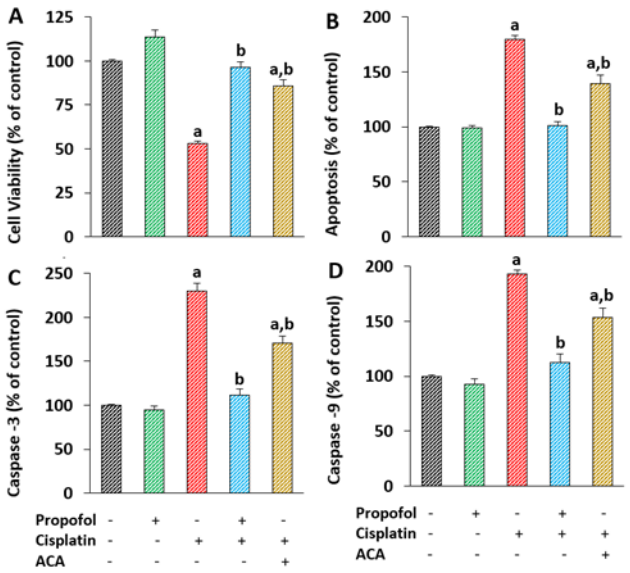

Figure 3. Cisplatin incubation-induced increases in apoptosis and caspases were diminished by the incubations with propofol and ACA (25 µM). (n = 3 and mean ± SD); **A**: Cell Viability; **B**: Apoptosis; C: Caspase-3; **D:** Caspase-9; ([a]p <0.05 *vrs*. CNT. [b]p <0.05 *vrs.* cisplatin).

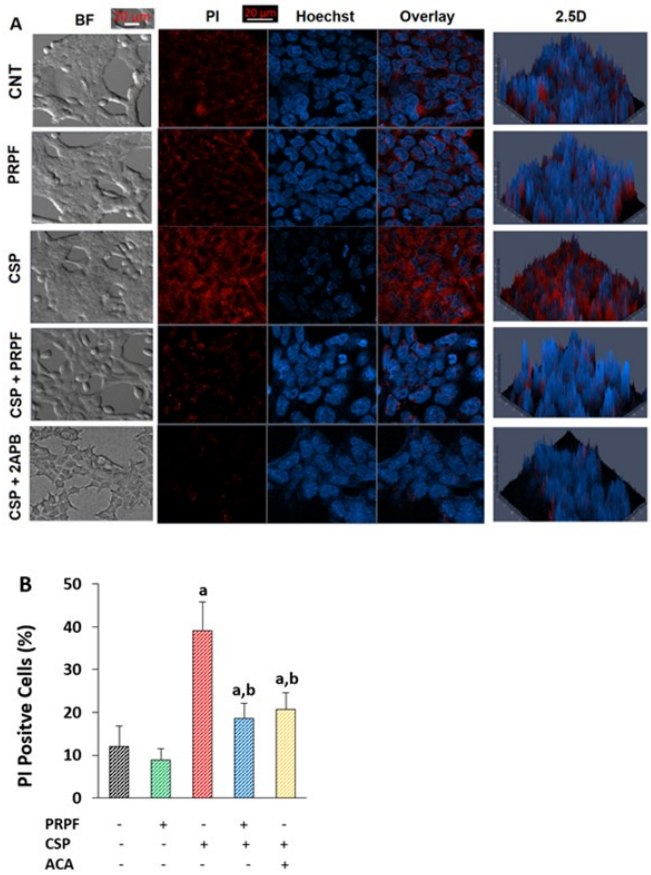

Figure 4. The percentage of PI-positive SH-SY5Y cells was increased by CSP, however this effect was mitigated by the incubation of PRPF. (Mean ± SD); **A**: BF: Bright field, red (PI), blue (Hoechst), overlay, and 2.5D images; **B**: The average percentage changes of PI-positive cells. ([a]: p <0.05 *vrs.* CNT and PRPF; [b]: p <0.05 *vrs*. CSP).

The orange (JC-1), green (DCFH-DA), overlay, and 2.5D (Figure 5A) pictures were saved in the LSM-800 microscope. The mean values of JC-1 (Figure 5B) and DCFH-DA (Figure 5C) were upregulated after CSP incubation ($p < 0.05$). However, the impact of CSP was reduced ($p < 0.05$) by PRPF and 2APB by preventing the production of ROS and mHP in the SH-SY5Y.

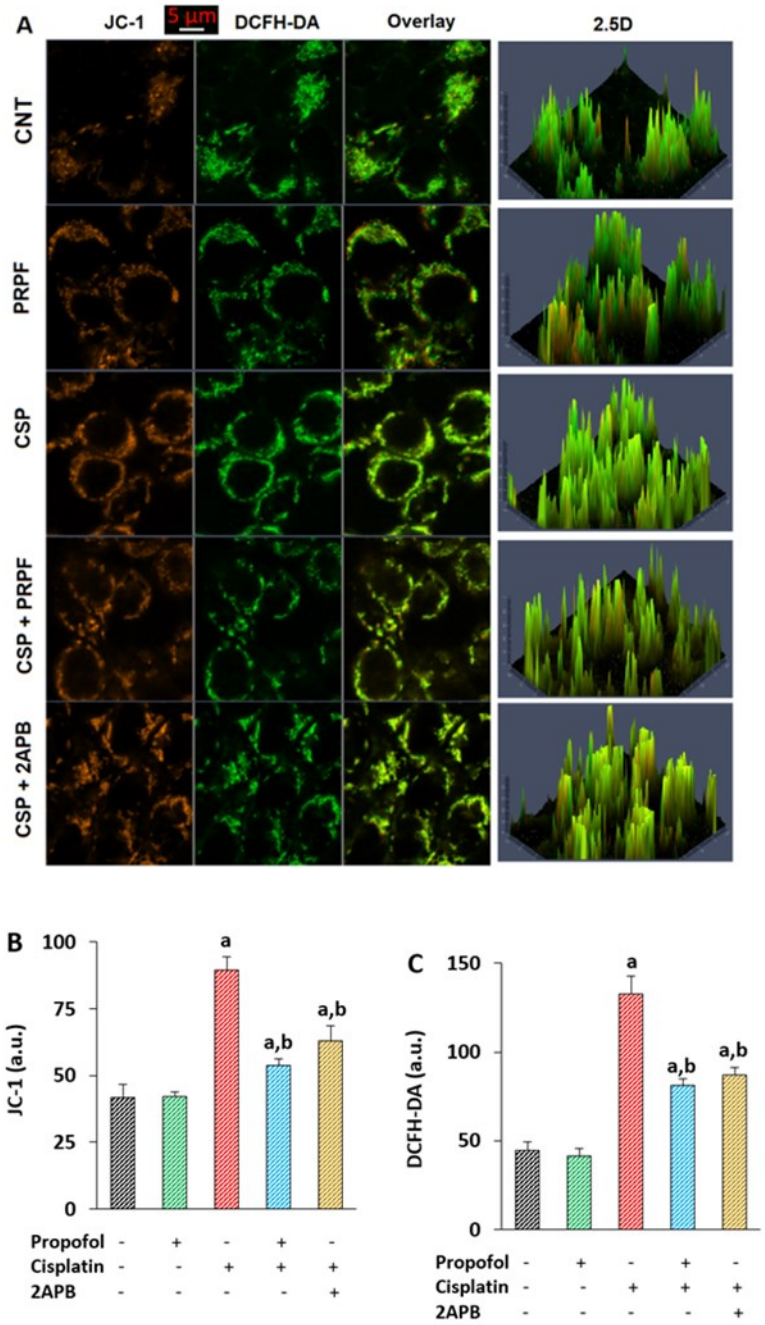

Figure 5. Propofol (200 µM) changed the effects of cisplatin (25 µM) and led to a decrease in ROS and mitochondrial membrane hyperpolarization (mHP). (Mean ± SD); (**A**). The JC-1 (**B**) and DCFH-DA (**C**) mean values are expressed as an a.u.; Scala bar = 5 µm. ([a]$p < 0.05$ *vrs.* CNT and PRPF; [b]: $p < 0.05$ *vrs.* CSP).

DISCUSSION AND CONCLUSION

In the current study. I noticed that the administration of PRPF to the neuronal cells reduced the CSP-mediated elevation of oxidative neurotoxicity and neuronal death through the suppression of TRPM2.

Vitamin E is thought to possess similar properties and could be the source of the PRPF effect.[8,11] Vitamin E and other antioxidants were utilized to inhibit the TRPM2 channel.[3,4,25] According to the current findings, the mHP and ROS of the PRPF treatment group decreased as a result of CSP. It has been demonstrated that many antioxidants offer a variety of protective advantages against harm induced by CSP.[8,10,14,26] Research on SH-SY5Y cell lines and animal hippocampal neurons has demonstrated that PRPF possesses anti-apoptotic and ROS inhibitory characteristics.[8,15]

In the current investigation, I found that PRPF inhibited TRPM2 current density in the cells, which reduced $[Ca^{2+}]_i$, ROS and apoptosis caused by CSP. With the exception of the TRPM2 channel in neural cells, the regulatory function of PRPF has been documented in NMDA receptors and TRP channels. According to the current findings, PRPF inhibited the NMDA receptor in the parenchymal arterioles and hypoglossal motoneurons of the rat brain, which also decreased oxidative stress.[16-18] It is demonstrated that PRPF inhibits the rise in $[Ca^{2+}]_i$ amount caused by NMDA receptor activation in cultivated rat hippocampal neurons.[19] The findings of a recent study showed that PRPF promoted cardioprotection in rats by inhibiting TRPV1.[20] The TRPA1-mediated nitric oxide generation was decreased in the DRG cell line by blocking TRPV1.[20] Activating the TRPV1 channel in the mouse and human DRGs, PRPF increased pain sensitivity, in contradiction to earlier findings.[21,22] As a result, multiple cell-specific mechanisms, including ROS, apoptosis, and TRPM2-stimulation, may be at work when PRPF affects cells.

When CSP is administered, an increase in mitochondrial Ca^{2+} uptake in SH-SY5Y, glioblastoma, and kidney cells causes an increase in the production of ROS and cell death indicators (PI positive cell percentage, apoptosis, caspase -3, and -9) that are caused by mHP.[11,13,14] TRPM2 stimulator effects of CSP on SH-SY5Y cells have been documented.[14] Consequently, the actions raise mHP, which in turn causes the ROS and cell death markers to be upregulated.[4] On the other hand, the suppression of TRPM2 lowers the percentage of PI positive cells, apoptosis, and ROS formation in neuronal cells, including SH-SY5Y.[4,26] Based on the available data, the elevation of mHP in SH-SY5Y was caused by CSP-induced TRPM2 activation (by excess Ca^{2+} influx). This, in turn, led to the overexpression of ROS, cell death, and apoptosis through the rise of caspase -3 and -9, but a decrease in cell viability. Treatment with PRPF and TRPM2 blockers (ACA and 2APB) modulated the alterations. The current findings show that in mouse hippocampus HT22 cells, PRPF therapy reduced cytokine-induced increases in mitochondrial dysfunction, nitric oxide, caspases, and mitochondrial Ca^{2+} buildup.[27] During oxygen glucose deprivation/reperfusion damage, PRPF improved cardiomyocyte cell survival, reduced ROS and mitochondrial dysfunction levels, and prevented apoptosis, caspase -3, and caspase -9.[28] PRPF attenuates H_2O_2-induced ROS and apoptosis (caspase -3 and caspase -9) via the stimulation of mitochondria dysfunction-mediated pathways and antioxidants such as glutathione and superoxide dismutase in neonatal rat cardiomyocytes.[29] In contrast to the results, the experimental animal studies report that administration of PRPF causes brain cell death and neurodegeneration in neonatal rats.[30]

In conclusion, due to the downregulation of TRPM2 stimulation-induced neuronal damage, SH-SY5Y cells were protected from CSP-mediated apoptosis, cell death, and oxidative mediators by incubating PRPF through the attenuation of TRPM2. CSP-induced oxidative damage may be caused by activating TRPM2-mediated excessive Ca^{2+} influx, apoptotic, and oxidant mediators, even if PRPF treatment decreases CSP-induced oxidative neurotoxicity and apoptosis. Further studies in mouse neurons are required to completely understand the molecular and cellular mechanisms behind the identified role of PRPF in TRPM2 stimulation-mediated oxidative and apoptotic neurotoxicity.

Ethics Committee Approval: There are no human and animal data available. This study doesn't need to have ethics committee approval.

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

Author Contributions: Concept – HÖO; Supervision – HÖO; Materials – HÖO; Data Collection and/or Processing – HÖO; Analysis and/or Interpretation – HÖO; Writing – HÖO.

Peer-review: Externally peer-reviewed.

Financial Support: A company **(**BSN Health) provided financial support for this study (Project No: 2023-03). The project is owned by Dr. HÖO.

Acknowledgment: Technician Muhammet Şahin (BSN Health, Analyses, Innov., Consult., Org., Agricul., Trade Ltd., Isparta, Turkiye) and technician Fatih Şahin are appreciated by the authors for their help with the LSM-800 laser confocal microscopy analyses, electrophysiology, and plate reader.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):263-271 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):263-271*

Catheter Selection in Home Parenteral Nutrition Patients and Noteworthy Definitions in The Diagnosis of Catheter Infections

Evde Parenteral Nütrisyon Hastalarında Kateter Seçimi ve Kateter Enfeksiyonu Tanısında Öne Çıkan Tanımlar

[1]Ali TAMER, [1]Tunahan ZENGİN, [2]Oğuz KARABAY

[1]Department of Internal Medicine, Sakarya University Faculty of Medicine, Sakarya, Türkiye
[2]Department of Infectious Diseases and Clinical Microbiology, Sakarya University Faculty of Medicine, Sakarya, Türkiye

Ali Tamer: https://orcid.org/0000-0003-2005-0737
Tunahan Zengin: https://orcid.org/0009-0007-4335-8781
Oğuz Karabay: https://orcid.org/0000-0003-1514-1685

ABSTRACT
The rising number of patients in need of long-term parenteral nutrition has necessitated home parenteral nutrition. Extended usage of central venous catheters and parenteral nutrition has given rise to its own complications. Among them, catheter-related bloodstream infections (CRBSI) are linked to life-threatening complications, especially sepsis, septic shock, and metastatic infections. The principal objective of this review is to define diagnostic methods, notable clinical and laboratory findings, and catheter salvage strategies towards preventing CRBSI, which include defining and interpreting blood culture and its results, its confounding variables and common shortcomings in routine practice. We will discuss the types and relative advantages and disadvantages of differing methods of central venous access and compare the common diagnostic definitions used by existing guidelines. CRBSI remains a serious complication, and we aim to debate when timely intervention will be necessary in light of the existing literature.
Keywords: Catheter-related infections; parenteral nutrition, home; sepsis

ÖZ
Uzun süreli parenteral beslenmeye ihtiyaç duyan hasta sayısının artması, evde parenteral beslenmeyi zorunlu hale getirmiştir. Uzun süreli santral venöz kateter kullanımı ve parenteral beslenme kendi komplikasyonlarına yol açmıştır. Bunlar arasında kateterle ilişkili kan dolaşımı enfeksiyonları (KİKDE), özellikle sepsis, septik şok ve metastatik enfeksiyonlar gibi yaşamı tehdit eden komplikasyonlarla ilişkilidir. Bu derlemenin ana odağı, kan kültürünün ve sonuçlarının tanımlanması ve yorumlanması, kafa karıştırıcı değişkenler ve rutin uygulamadaki yaygın eksiklikler, KİKDE'yi önlemeye yönelik tanımlar, tanı yöntemleri, önemli klinik ve laboratuvar bulguları ve kateter kurtarma stratejileridir. Farklı santral venöz erişim yöntemlerinin türlerini, göreceli avantaj ve dezavantajları ve mevcut kılavuzların kullandığı tanı kriterleri kıyaslanacaktır. KİKDE ciddi bir komplikasyon olmayı sürdürmektedir ve mevcut literatür ışığında zamanında ivedi müdahalenin ne zaman gerekli olacağını tartışmayı amaçlıyoruz.
Anahtar Kelimeler: Evde parenteral nütrisyon, kateter ilişkili enfeksiyon, sepsis

Sorumlu Yazar / Corresponding Author:
Ali Tamer,
Sakarya University Faculty of Medicine, Department of Internal Medicine, Sakarya, Türkiye
Tel: +90 5335400368
Email: tamer@sakarya.edu.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 19/04/2024
Kabul Tarihi/ Accepted: 10/06/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf/ Cited: Tamer A and et al. Catheter Selection in Home Parenteral Nutrition Patients and Noteworthy Definitions in The Diagnosis of Catheter Infections. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):263-271. doi: 10.26453/otjhs.1470669

INTRODUCTION

Long-term Central Venous Catheter (CVC) application was first begun in 1973 by Dr. Broviac. Implanted Ports were developed in 1982, and multiple lumen catheters were developed in 1983.1 At first, CVCs were used for central venous pressure monitoring, hyperalimentation and bone marrow transplantations.[2] Later, they began to be used for haemodialysis, ICU, chemotherapy and long-term parenteral nutrition. Peripherally inserted central catheters (PICC), tunnelled and non-tunnelled catheters and port systems were developed for convenience. But despite the benefits of catheter use, their infectious and non-infectious complications continue to pose problems.

Parenteral nutrition (PN) encompasses the methods used for parenteral supplementation of macronutrients and micronutrients in cases where enteral nutrition (EN) is inapplicable or insufficient. Long-term PN has necessitated home parenteral nutrition (HPN). It's known that PN products also contribute to catheter usage complications.[3]

Intestinal failure (IF) was defined in 1981 by Fleming and Remington as "a reduction in the functioning gut mass below the minimal amount necessary for adequate digestion and absorption of nutrients".[4] IF is defined as gut function below the requisite threshold for the absorption of macronutrients and/

or electrolytes to the point of requiring intravenous intervention in order to continue health and/or growth.[5] A gut function reduction that does not require any intravenous (IV) intervention for continued health and/or growth is considered as intestinal insufficiency. IF is classified under; functional classification (type 1 acute and short-term conditions, type 2 prolonged acute conditions and type 3 potentially chronic conditions), pathophysiological classification (short bowel, intestinal fistula, intestinal dysmotility, mechanical obstruction and extensive small bowel mucosal disease), clinical classification (on the basis of requirements for energy and the volume of IV supplementation), anatomical classification (end-jejunostomy with no colon in continuity, jejunocolic anastomosis with no ileo-cecal valve and a part of the colon in continuity, and jejunoileal anastomosis with both the ileo-cecal valve and the entire colon in continuity). Patients with irreversible IF are most likely to need long-term or lifelong HPN or intestinal transplantation.[6]

Therefore, for some patients, HPN therapy is a vital treatment. In the treatment of HPN, CVCs and PVCs play a critical role. However, catheter-related bloodstream infections (CRBSI) are linked to life-threatening complications, especially sepsis, septic shock, and metastatic infections.[7,8]

The primary focus of this review is definitions, diagnostic methods, notable clinical and laboratory findings and catheter salvage strategies towards preventing CRBSI. Ethics committee approval was not obtained. The editor invited me to review. Ethics committee approval is not required.

TYPES OF CATHETERS

Although peripheral application appears suitable for short-term PN, the requirement for high-volume, high-osmolality nutrition, the inability of peripheral cannulas to remain open for longer than 14-21 days, the fact that many patients requiring HPN have damaged peripheral vessels and the risk of thrombophlebitis means peripheral application seems inappropriate for PN. This necessitated the development of central venous access catheters despite their own life -threatening risks.[9]

Venous access via large diameter veins and high rate of flow has begun with arterio-venous shunts and was further developed through teflon, silicone and elastomer catheters.[10]

Catheters developed for PN applications are examined in two groups: peripheral and central. Peripheral venous catheters (PVC) are placed within veins of the forearm or hand for very short-term use. Midline catheters (MC) and long peripheral catheters (LPC) (7.6–20.3 cm long that do not reach the central veins, for use longer than 6 days and are limited to weeks) are used by placing them into the proximal basilic or cephalic veins through the antecubital fossa. CVCs are for short-term use (non-tunnelled) and PCVC (reaches the superior vena cava through the cephalic and basilic veins) and for long-term use (tunnelled) and ports.[11]

Catheters are classified based on their compositions as Teflon, silicone, polyurethane, polyvinyl chloride or polyethylene. Polytetrafluoroethylene (Teflon) or polyurethane catheters are correlated with fewer infectious complications compared to polyvinyl chloride or polyethylene catheters. Steel needles used for peripheral venous access as an alternative to catheters have the same risk of infectious complications as Teflon catheters.[12,13] The development of silicone catheters has reduced the risk of complications.[14]

PVC's MC; 20 cm and LPC (3 Fr, 8 cm; 4 Fr, 10 cm; 4 Fr, 18 cm) are polyethylene in structure.[15,16] In suitable patients, they might be correlated with fewer complications when compared to CVCs, but the risk of catheter infection should be considered.[17]

PCVC can be recommended in elderly or patients otherwise considered unable to use the catheter, patients with Short Bowel Syndrome (SBS) with gut continuity reconstruction planned in 3-6 months, and patients with malignancy (with expected remaining lifespan over 2-3 months).[10]

Broviac and Hickman's catheters are similarly structured catheters with different lumen diameters. The lumen diameter of paediatric Broviac's' is 0.12 mm, Broviac catheters' is 0.2 mm, and Hickman catheters' is 0.32 mm. Additionally, the external side of the Hickman catheter does not have a Teflon covering. Hickman catheter is primarily used in patients who often require chemotherapeutic agents or blood and blood product transfusions and require frequent blood draws.[18] Broviac catheter is 90 cm in length and crafted from silicone rubber (Silastic). The intravenous segment of the catheter is thin and elastic enough to float inside the superior vena cava. It is tied to a thicker extravascular segment through a Dacron cuff. The extravascular portion is stationed inside a subcutaneous tunnel. Dacron cuff causes a fibrotic tissue formation which ensures better adhesion of the catheter and contributes to the barrier formation against the passage of microorganisms.[19]

Surgically implanted totally implantable venous access devices (TIVADs) are comprised of a tunnelled silicone catheter and a subcutaneously implanted port reservoir.[11] Implantable systems have the advantages of a better cosmetic appearance, less migration, less occlusion and fewer catheter infections. The port reservoir consists of a stainless-steel chamber, conically shaped, with an inner diameter measuring 1.02 mm and an outer diameter of 2.8 mm, an inner volume of 0.4 ml, and a self-sealing membrane made of silicone rubber that may be

pierced up to 2000 times with a 22 GA Huber needle, and which is connected to the cone and then connected to a small, stainless-steel chamber. It features a silicone rubber radiopaque catheter blocked by a steel cylinder. This technique is recommended in patients that don't need HPN every day.[20]

Arteriovenous fistula could be used when long-term home parenteral nutrition is necessary. But in this regard sufficient evidence does not exist for clear recommendations. It may be deemed appropriate for specific patients to prevent catheter-related infections.[12,21]

CATHETER SELECTION AND INSERTION

For non-tunnelled catheters left-side subclavian path is preferred due to minimal infection risk. In contrast, for tunnelled catheters, although no priority insertion path is recommended (subclavian, internal jugular, external jugular), the left-sided subclavian catheter can be preferred due to less mobility (except haemodialysis and advanced renal failure patients). The femoral path is relatively contraindicated due to thrombosis and infection risk. The minimum amount of lumened catheters and the use of ultrasound during catheter insertion lowers the risk of complications.[7,13,19] Catheter choice should be made in accordance with the duration of the intravenous treatment. PCVCs are generally preferred in patients requiring short-term (<3 months) HPN treatment. Due to the risk of CRBSI, tunnelled catheters are most frequently preferred.[8,13]

CATHETER-RELATED BLOODSTREAM INFECTIONS

For some patients, i.e., those with specific medical conditions such as short bowel, HPN therapy is a vital treatment. In the treatment of HPN, CVCs and PVCs play a critical role. However, catheter-related bloodstream infections (CRBSI) are linked to life-threatening complications, especially sepsis, septic shock, and metastatic infections.[7,8]

CRBSIs may arise from bacterial or fungal origins, but the majority of these problems arise from the patient's skin flora. The area where the catheter comes into contact with the skin is considered a frequent cause of endo-luminal (inside the catheter) infections, while infections originating from the catheter exit site or tunnel tract are regarded as extra-luminal (outside the catheter) infections in nature. CRBSIs are also categorised based on the total span of the episodes as transient, intermittent or persistent (sustained transfer of microorganisms into the bloodstream from an intravascular source) and community- or hospital-acquired (detected within 72 hours of hospitalization).[22–24]

Extra-luminal catheter related infections typically occur within the initial week of catheter insertion. Internal lumen infections generally occur after a week as the number of manipulations increases. The onset of infection in long-term catheters usually occurs within a span of 10 days, indicating that the inner lumen is the leading site for CRBSI.

This article focuses on the definition and management of CRBSIs, aiming to provide a scientific guide to the effective handling of such infections.[6,11,13,14,25]

Table 1. Definitions.

Terminology	Definition
Phlebitis	Erythema, temperature increase, and pain or tenderness are detected in the path of a catheterized vessel.
External Site Infection	Redness, swelling, and/or pain within 2 cm of the catheter exit site. It may also contain microbiological findings.
Tunnel Infection	Tenderness, erythema and/or swelling are detected in the subcutaneous path of the tunnel catheter more than 2 cm from the catheter exit point.
Pocket Infection	Infected fluid is present in the subcutaneous compartment of a fully implanted intravascular device.
Catheter Colonization	Significant growth of microorganisms on the tip of the catheter, subcutaneous portion of the catheter or catheter hub.
Infection Related to Possible LCBSI	It is defined when there are no signs of systemic or local infection despite the presence of microorganisms in blood cultures taken from samples.
Bloodstream Infection	- Infusate Related: Suspicion regarding contaminated infusion should arise when there is no other infection that could explain BSI or when the sudden onset of shock occurs during parenteral drug or fluid infusion. - Catheter-Related: CRI is a clinical condition manifested by clinical symptoms, biochemical infection parameters and blood culture positivity.
Recovery	It is defined as clinical and biochemical improvement 1 to 2 weeks after discontinuation of CRBSI antibiotherapy.
Relapse Infection	It means reinfection within 30 days. It is defined as an infection arising within the next 30–100 days with the same causative pathogen and an identical antibiogram.
Complicated CRI	It is considered complicated when persistent fever (72 hours), positive follow-up blood cultures (48 hours), septic shock (septic) thrombophlebitis, endocarditis, and/or other metastatic infectious foci are present.

LCBSI: Laboratory Confirmed Bloodstream Infection; MBI-LCBSI: Laboratory Confirmed Bloodstream Infection with Mucosal Barrier Injury; BSI: Bloodstream Infection; CRI: Catheter-Related Infection; CRBSI: Catheter-Related Bloodstream Infection; NHSN: National Healthcare Safety Network; CVC: Central Venous Catheter; CVC-BSI: Central Venous Catheter-Related Bloodstream Infection; IWP: Infection Window Period; ED: Event Date.

Table 1. Continue.

CVC Rescue	Preservation of venous access during a CRI. It is considered successful if the catheter remains for at least 60 days after starting CRI treatment and there is no recurrence or relapse.
Infection Window Period (IWP)	It is defined as 7 consecutive days during which all criteria for site-specific infection must be fulfilled. This period encompasses the collection date of the initial positive diagnostic test. 3 calendar days before and 3 calendar days after are used as an element that meets site-specific infection criteria.
Event Date (ED)	The first date on which the first element is used to meet an NHSN site-specific infection criterion occurs within the seven-day infection window period. If the OT is determined to be one of the two days before hospitalization, the date of the event is considered admission day 1.
Healthcare-Associated Infection (HAI)	An infection is considered a healthcare-associated infection (HAI) if the event date is considered on or after calendar day 3 of admission to an inpatient facility.
Secondary BSI Attribution Time	The amount of time a blood sample must be collected before a secondary bloodstream infection can be attributed to a primary site infection. It is 14-17 days long, depending on the date of the event (3 days before, 13 days after the event)
Recurrent Infection Time Period (RITP)	A period of 14 days in which no new infections of the same type are reported. The date of the event is Day 1 of the 14-day RITP. If criteria are met for the same type of infection and the event date is within a 14-day RIT, it will not be considered a new event.
Primary BSI	LCBSI is not secondary to an infection in another body site. (Secondary Specific Types of Infections, urinary tract infection, pneumonia, and surgical site infection).
Secondary BSI	A BSI is considered to originate from a site-specific infection in another body part.
CVC-BSI	Indicates LCBSI where a suitable BSI organism has been identified and a suitable central line is present at or the day before the LCBSI ED. In cases where LCBSI criteria are met, MBI-LCBSI status should be evaluated.
LCBSI 1	Identified by a culture obtained from one or more blood samples OR identified to the genus or species level by non-culture-based microbiological testing. The organism(s) detected in the bloodstream are not associated with infection at another site.
LCBSI 2	A patient of any age that exhibits at least one of the following signs or symptoms: fever (>38.0 °C), chills, or hypotension AND the organisms identified in the blood are not associated with infection at another site AND cultures are obtained from two or more blood samples collected on separate occasions. The criteria elements must occur within the 7-day IWP from the date of collection of the positive blood sample.
LCBSI 3	A patient younger than one year of age exhibiting at least one of the following signs or symptoms: fever (>38.0 °C), hypothermia (<36.0 °C), apnea, or bradycardia AND the organism(s) identified in the blood are not associated with infection at another location AND criterion items must occur within the 7-day IWP.
MBI-LCBSI	A BSI event must fully meet the criteria for an LCBSI before considering the corresponding MBI-LCBSI criteria. MBI-LCBSI ED will always be the date on which the prerequisite LCBSI criteria are met. MBI-LCBSI is a subset of LCBSI criteria.
MBI-LCBSI 1	Defined as patients of all ages identified by culture or non-culture microbiological testing of at least one blood sample, with intestinal organisms ONLY.
MBI-LCBSI 2	Patients of all ages with at least two matching blood samples with ONLY Viridans Group Streptococcus and/or Rothia spp. alone but no other organism
MBI-LCBSI 3	. Patients younger than 1 year old with at least two matching blood samples identified only for S. viridans and/or Rothia spp.

LCBSI: Laboratory Confirmed Bloodstream Infection; MBI-LCBSI: Laboratory Confirmed Bloodstream Infection with Mucosal Barrier Injury; BSI: Bloodstream Infection; CRI: Catheter-Related Infection; CRBSI: Catheter-Related Bloodstream Infection; NHSN: National Healthcare Safety Network; CVC: Central Venous Catheter; CVC-BSI: Central Venous Catheter-Related Bloodstream Infection; IWP: Infection Window Period; ED: Event Date.

The following terms and definitions (Table 1) contain critical information used in identifying, monitoring, and treating bloodstream infections.[6,7,11,25–27]

DEFINITION OF CONTAMINATION IN BLOOD CULTURES

Contamination refers to a situation that causes growth in culture results even though the organism in question can't be isolated from the blood sample. The majority of contamination cases occur as a result of microorganisms found in the skin flora contaminating blood culture bottles.

MISTAKES INCREASING BLOOD CULTURE CONTAMINATION

Inadequate skin antisepsis (lack of contact time or new contact), improper preparation of blood culture bottles (lack of cap disinfection), syringe needle exchange with multiple interventions, and blood collection from intravenous catheters (inoculation) errors often occur in the preanalytical process and increase the risk of contamination.

MICROBIOLOGICAL DEFINITION OF CONTAMINATION

Contamination is defined when one or more skin microbiota member microorganisms are found growing in only one of the patient's multiple blood

culture sets (e.g., in one or more bottles of one set, in one of two sets, in one of three sets). The patient should not have any clinical manifestations or microbiological evidence of infection with these microorganisms. In addition, the proliferation of bacteria native to the skin microbiota in the peripherally drawn blood culture when the intravascular catheter cultures are negative, or the differences in the isolated bacteria from each other when the intravascular catheter cultures and peripheral vein cultures are positive can be given as examples of contamination.

DIFFERENTIATION OF CAUSATIVE AGENTS AND CONTAMINATION IN BLOOD CULTURES

To differentiate between the agent and contamination, the same agent must be isolated in blood cultures taken from at least two separate veins (if species-level identification and antimicrobial sensitivity are the same). When a possible contaminant is detected in the first blood culture, the isolate is best retained until the outcomes of other blood cultures are obtained. If other blood cultures produce the same agent, they should be regarded as causative and reported. However, if the identification or susceptibility results are different, the isolated bacteria should be considered contaminants. In the case of growth of important microorganisms (e.g., C. albicans, group A streptococci, and Gram-negative bacilli), these elements ought to be considered, even when the colony count is <15 cfu.

CONTAMINATION RATES AND IMPORTANT MICROORGANISMS

Contamination is detected in approximately one-third of positive blood cultures. Decreasing the amount of blood taken heightens the risk of contamination. Additionally, aside from the skin microbiota, some microorganisms that can temporarily colonise (Acinetobacter spp., C. perfringens, etc.) may cause contamination in blood cultures if appropriate skin antisepsis is not performed. Members of the skin microbiota considered to be contaminated include coagulase-negative staphylococci (CoNS), Corynebacterium species (except C. jeikeium), Bacillus species (except B. anthracis), Micrococcus species, Aerococcus species, and Cutibacterium species.[11,22–26]

CATHETER AND BLOOD CULTURES IN DIAGNOSIS

Once adequate skin preparation has been performed, paired samples from the catheter and a peripheral vein should be acquired for culturing before starting antibiotics. Diagnostic testing for vascular catheter-associated infection should not be performed without a high suspicion of CRBSI. However, it may be recommended that patients without CRSBI undergo screening tests every 3 months if their risk of CRBSI is high.

In general, the most precise approach for diagnosing CRBSI is quantitative blood cultures. For CRI, catheter culture, peripheral blood culture, differential time (DT) when the catheter is preserved, cast plate, catheter tip culture when the catheter is removed, and if the port is removed (port reservoir content as well as the catheter tip) methods can be used.[28] A sample should be collected for Gram staining and culture when CRI is suspected, and exudate is noted at the catheter exit site. Studies show that the DT test has an overall sensitivity of 96.0% and is as high as 100% when there is no delay in collecting, transporting, and loading blood culture bottles into the analyzer. Delays in loading blood culture bottles (>4 hours) have a greater impact on reducing sensitivity than delays in collecting central and peripheral blood samples (>10 minutes).[28,29]

BLOOD CULTURE IN THE DIAGNOSIS OF FUNGI

Laboratory practices required for blood culture collection and processing are similar for cases with bacteremia and candidemia. The sensitivity of blood culture in diagnosing candidemia is 50-75%. Therefore, if candidemia is suspected and no mycotic growth can be noted in the blood cultures, auxiliary diagnostic tests should be used. Generally, for mycotic blood culture bottles, the time needed is at least three weeks.

RAPID ANTIMICROBIAL SUSCEPTIBILITY TESTING FROM BLOOD CULTURE BOTTLES

A further period of 24-48 hours is required for passages from blood culture bottles following the growth signal and for antimicrobial susceptibility testing (AST) by traditional definition. Disc diffusion test is a standardised, easy-to-apply, cheap, repeatable and reliable test that does not demand additional devices and equipment to obtain AST results in all medical microbiology laboratories. On the other hand, with EUCAST-HADT, results are obtained in 8 hours. This is imperative for the early intervention of patients in critical condition.[22–24,28]

INCONSISTENT RESULTS

If the initial culture signal is positive and no growth occurs in the passage despite the Gram staining result being positive, anaerobic bacteria that grow poorly or slowly should be considered. If a positive signal is received, but the Gram staining is negative or no growth is noted in the passage, the breeding curve should be examined in detail using automated systems. If the growth curve shows microbial

growth, different staining methods, such as carbol fuchsin, Giemsa, acridine orange, can be used. This can also guide the selection of supplementary culture medium.[11,22–24]

CULTURING PROCEDURE

In adults, the optimal volume of blood to be collected for each blood culture set is 20-30 mL. The blood taken from the catheter and the periphery should be the same volume. The location (catheter/periphery) and the time of blood collection must be recorded on blood culture bottles. The standard incubation period in automated blood culture systems is five days. A blood culture set should contain one of each of the aerobic and anaerobic bottles (except for paediatric patients). Compared to sets containing only aerobic bottles, the use of sets containing both aerobic and anaerobic bottles enables the detection of obligate anaerobic bacteria and faster growth of some facultative anaerobic bacteria and C. glabrata.[11,22–24]

When performing more than two separate blood draws on the same or consecutive calendar days, separate field preparation or blood cultures should be assigned different numbers during blood or sample collection. These samples are processed separately and reported separately in the final laboratory report. Blood culture bottles should be delivered to the laboratory within two hours after blood collection and should be preserved at room temperature during transportation. Transfer of vials to the laboratory should be done using an appropriate method and transport container.[25]

CATHETER-RELATED BLOODSTREAM INFECTION DIAGNOSIS

Definitions of CRI vary across different sources, making comparison difficult. Standardised definitions for catheter-related infections have been offered by the Centers for Disease Control and Prevention National Healthcare Safety Network (NHSN), and the Infectious Disease Society of America (IDSA). While the NHSN definition for CRBSI is used for surveillance purposes, the IDSA criteria for CRBSI are used for narrower diagnostic purposes. In this review, definitions of catheter-related infections were evaluated and categorised as follows:

- Catheter-Associated Bacteraemia (CAB): Isolation of the same organism in semi-quantitative or quantitative cultures of blood drawn from a peripheral vein as well as the catheter lumen.
- Catheter-related bloodstream Infection (CRBSI): It is characterised as the same organism being isolated in semi-quantitative or quantitative cultures of blood taken from both the catheter lumen and the peripheral vein and the presence of clinical symptoms of bloodstream infection in the patient. It is considered to indicate CRBSI if the colony count of a blood sample taken from the catheter lumen numbers more than thrice the colonies compared to the blood taken from a peripheral vein or if the number of colonies of a blood sample taken from a lumen number more than thrice the colonies of a blood sample taken from the second lumen. According to the IDSA definition, quantitative blood cultures taken from the catheter and peripherally, where blood taken from the catheter produces 3 times more colonies than peripheral blood, and microbial growth in blood taken from a catheter can be identified at least 2 hours before microbial growth can be identified in blood samples taken from a peripheral vein best defines CRBSI.
-No criteria: A condition that does not fit a standard definition for CRI.[11,13,26,30,31]

DIAGNOSIS IN CASE OF CATHETER REMOVAL

When it is decided that the catheter needs to be removed, first, a pair of blood cultures should be taken from the catheter and the periphery. Additionally, the removed catheter should also be sent to the laboratory for culture. Catheter culture can be obtained in two ways:

1. Short-Term Catheters (less than 14 days): The "roll plate" method is advised for routine clinical microbiological analysis for the tip of such catheters. In this method, a 5 cm segment taken from the distal end of the catheter, removed aseptically, is rolled back and forth 4-5 times on a blood agar surface and sown. The fact that >15 cfu grew at the end of incubation and that the growing microorganism was similar to that in peripheral blood culture would indicate that the catheter is not the root of the bloodstream infection.
2. Long-Term Catheters (≥14 days duration): For these types of catheters, semiquantitative growth of the same microorganism from both insertion site and catheter hub cultures at <15 cfu/plate indicates that the catheter is not the root of the bloodstream infection. The most accurate diagnostic approaches for identifying microorganisms on both the interior and exterior of the catheter are quantitative catheter culture techniques (luminal washing or sonication procedures), which also have higher specificity than qualitative fluid cultures.

DIAGNOSIS OF CRBSI IN CATHETER PRESERVED CASES

In cases where automated blood culture systems are used: A minimum of two sets of blood cultures are obtained concurrently or consecutively, one sample collected from the peripherally and the other from the catheter lumen or port chamber. If the same type of microorganism is isolated from both sets with

identical AST results and there is no other focus of infection, CRBSI can be considered.[11,22–24,32–34]

Delays in confirmation of CRBSI can be solved by methods such as rapid gram or acridine staining of cultures[32]. Acridine orange leukocyte cytospin (AOLC) and PCR targeting bacterial 16S ribosomal DNA are other tests used in the diagnosis of CRI but are not routinely used in clinical microbiology laboratories.[9,35]

Antimicrobial coatings may cause false negative culture results. For catheters coated with silver sulfadiazine or chlorhexidine, particular inhibitors can nullify this drawback, whereas the same does not apply to catheters coated with minocycline or rifampin.

CATHETER-ASSOCIATED SKIN INFECTION

If sepsis is suspected at the skin entry point or tunnel of the catheter, external-hub swab culture and blood cultures are required. Positive results are important to determine the origin of CRI.

INTERPRETATION OF THE CRBSI DIAGNOSIS

The following criteria should be taken into consideration for the diagnosis of CRBSI:

- The first growth should be in the blood culture taken from the catheter.
- The difference between the positivity time of the blood culture taken from the periphery and the blood culture taken from the catheter should be at least 120 minutes.
- The difference between positivity times being less than 120 minutes does not exclude the diagnosis of CRBSI.
- If there is >100 cfu/mL bacterial or >25 cfu/mL fungal growth in the catheter blood, the diagnosis of CRBSI can be considered even if there is no growth in the blood culture taken from the periphery.
- When both blood cultures are negative, the diagnosis of CRBSI is not considered.[11,22–24,32]

DISCUSSION AND CONCLUSION

Catheter selection is very important to prevent catheter-related complications in patients undergoing HPN treatment. CRBSIs are associated with life-threatening complications, especially sepsis, septic shock, and metastatic infections. CRBSI definitions are important for both early diagnosis and catheter rescue approaches in these catheter-dependent patients. The definitions provide effectiveness in terms of both necessary and timely antibiotic use and cost, morbidity and mortality.

Ethics Committee Approval: The editor invited to review. Ethics committee approval is not required.

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

Author Contributions: Concept – AT, OK; Supervision – AT, Data Collection and/or Processing – AT, OK; Analysis and/or Interpretation – AT, OK, TZ; Writing –AT, OK, TZ.

Peer-review: Externally peer-reviewed.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):272-276 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):272-276*

Neuroendocrine Tumor Developing in the Rectal Mesentery: A Case Who Had Surgery Due to Appendiceal Neuroendocrine Tumor 13 Years Ago

Rektum Mezenterinde Gelişen Nöroendokrin Tümör: 13 Yıl Önce Apendiks Nöroendokrin Tümörü Nedeniyle Ameliyat olan bir Olgu

[1]Kağan GÖKÇE, [2]Demet DOĞAN, [3]Murat ÜNER

[1]Okan University, School of Medicine, Department of General Surgery, Surgical Oncology Unit, İstanbul, Türkiye
[2]Okan University, School of Medicine, Department of Radiology, İstanbul, Türkiye
[3]Okan University, Faculty of Medicine, Intern Dr, İstanbul, Türkiye

Kağan Gökçe: https://orcid.org/0000-0003-4712-0512
Demet Doğan: https://orcid.org/0000-0003-0792-9042
Murat Üner: https://orcid.org/0009-0004-5530-1051

ABSTRACT
In the gastrointestinal tract, Neuroendocrine Tumors (NETs) are most observed in the appendix. This study aims to present a 51-year-old male patient diagnosed with NET in rectal mesentery. In 2009, appendiceal NET was diagnosed after appendectomy. Then, a total mesocolonic right hemicolectomy was performed. In the examination conducted in June 2022, a mass lesion was detected on the right side of the pelvis, posterior to the seminal vesicle and anterolateral to the rectum, within the rectal mesentery. Diagnosis of NET was made with a transabdominal biopsy, and then an operation decision was made. The perioperative frozen section confirmed that the mass lesion was a NET with clean surgical margins. In patients with large tumor sizes or high-grade NET, postoperative treatment is continued with chemotherapy or chemoradiotherapy. The patient was administered chemotherapy after surgery and was followed up in the outpatient clinic.
Keywords: Appendix, neuroendocrine tumor, rectal mesentery

ÖZ
Gastrointestinal sistemde Nöroendokrin Tümörler (NET) en sık apendikste görülür. Bu çalışmanın amacı, 51 yaşında rektum mezenterinde NET tanısı koyulan erkek hastayı sunmaktır. 2009 yılında apendektomi sonrası apendiks NET tanısı koyulmuş. Ardından total mezokolonik sağ hemikolektomi uygulanmış. 2022 yılına kadar rutin takiplerinde patolojiye rastlanmayan hastanın 2022 Haziran ayında yapılan tetkiklerinde pelvisin sağ tarafında, seminal vezikülün posteriorunda ve rektumun anterolateralinde, rektum mezenteri içerisinde kitle lezyon tespit edildi. Yapılan transabdominal biyopside NET tanısı koyuldu ve operasyon kararı verildi. Periopreatif frozen section incelemede kitle lezyonun temiz cerrahi sınırlar ile rezeke edilmiş NET olduğu doğrulandı. Büyük tümör boyutuna sahip ya da yüksek dereceli NET'de ameliyat sonrası tedaviye kemoterapi veya kemoradyoterapi ile devam edilmektedir. Hastaya cerrahi sonrası kemoterapi tedavisi verildi ve poliklinik takibine alındı.
Anahtar Kelimeler: Apendiks, nöroendokrin tümör, rektum mezenteri

Sorumlu Yazar / Corresponding Author:
Kağan Gökçe,
İçmeler Mahallesi, Aydınlı Yolu Caddesi, Okan Üniversitesi Tıp Fakültesi Araştırma ve Uygulama Hastanesi, Patoloji Anabilim Dalı, No: 2, 34947 Tuzla-İstanbul, Türkiye
Tel: +90 5325810590
E-mail: kagangokce2023@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 15/01/2024
Kabul Tarihi/ Accepted: 07/03/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Gökçe K and et al. Assessing Neuroendocrine Tumor Developing in the Rectal Mesentery: A Case Who Had Surgery Due to Appendiceal Neuroendocrine Tumor 13 Years Ago. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):272-276. doi: 10.26453/otjhs.1420202

INTRODUCTION

According to the 2019 World Health Organization, neuroendocrine neoplasms of the appendix are classified as well-differentiated Neuroendocrine Tumors (NETs), poorly differentiated neuroendocrine carcinomas, and mixed neuroendocrine/non-neuroendocrine neoplasms. Well-differentiated NETs are the most common type, while poorly differentiated NETs are rare.[1]

According to the 2010 WHO classification, the Ki-67 index of NETs is < 20%, and the majority are grade 1 (G1) or grade 2 (G2). 95% are less than 2 cm in diameter, and NETs generally have a good prognosis.[2] However, lymph node involvement at diagnosis was reported to be between 11% and 49%. In addition, up to 10% of cases may present with distant metastases.[3,4]

In the gastrointestinal tract (GIT), NETs are most commonly observed in the appendix. In surgical practice, NET is most commonly encountered in

patients who underwent appendectomy with the preliminary diagnosis of acute appendicitis. NETs that develop in other parts of the GIT are less common. The probability of NETs occurring in appendectomies varies between 1-1.5%.[5]

In appendiceal NETs, a tumor size of 2 cm and above is determined as a bad prognostic outcome.[6] Therefore, right hemicolectomy with lymph node dissection is recommended if the tumor size is above 2 cm.[7] After the surgery, the patients must be followed up with laboratory, radiological, and endoscopic examinations. Grade, degree of differentiation, and lymphovascular invasion are other prognostic factors in NETs. 70% of appendiceal NETs are 1 cm or less in size; they are usually located at the distal part of the appendix, and the probability of metastasis is relatively low. The likelihood of metastasis for appendiceal NETs of 2 cm or more is around 20%.[8] While appendectomy is sufficient for NETs less than 1 cm, right hemicolectomy is necessary for NETs 2 cm and above. In appendiceal NETs between 1 and 2 cm, the decision should be made according to the histopathological characteristics of the tumor.[9]

In this study, we aim to present a 51-year-old male patient diagnosed with NET in the rectal mesentery 13 years after appendectomy and right hemicolectomy due to appendiceal NET, with all dedicated laboratory results and radiological findings. Based on the outcome of this case, we would like to highlight the importance of follow-up and medical treatment after surgery.

CASE REPORT

Ethics committee approval is not required. The patient/relatives have signed an informed consent/ consent form, and the study was conducted following the international declaration, guidelines, etc.

In 2009, a 38-year-old male patient underwent an appendectomy due to a preliminary diagnosis of acute appendicitis. After surgery, histopathological examination revealed appendiceal NET with a largest diameter of 2 cm. Then, a total mesocolonic right hemicolectomy was performed. 13 years later, in 2022, the patient was investigated for complaints of dysuria, and a 2.7 cm diameter mass lesion was detected on the right side of the rectal mesentery. There was uptake in the lesion of Gallium-68 PET/ CT (Figure 1).

Serum Chromogranin-A: 62 µg/l, Nse:7.5 µg/L, and urine 5 HIAA:31.6 µmol/24h values were within the normal range. Contrast-enhanced pelvic magnetic resonance examination was performed, and a 27x22x24 mm tumor was observed located in the posterior to the seminal vesicle and anterolateral to the rectum and was close to the surrounding tissues but did not invade any surrounding tissue (Figure 2). The tumor is hypointense on T1-weighted images, hypointense on T2-weighted images, and shows mild diffusion restriction on diffusion-weighted images. The mass shows linear mild contrast enhancement in post-contrast images. Anteriorly, the mass was close to the seminal vesicles. However, no apparent signs of invasion were detected.

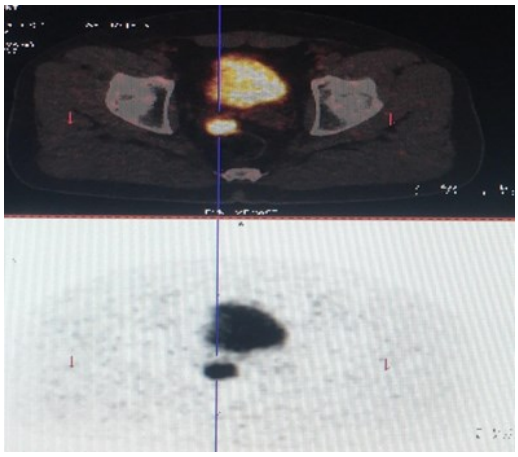

Figure 1. Uptake in the lesion in Gallium-68 PET/CT.

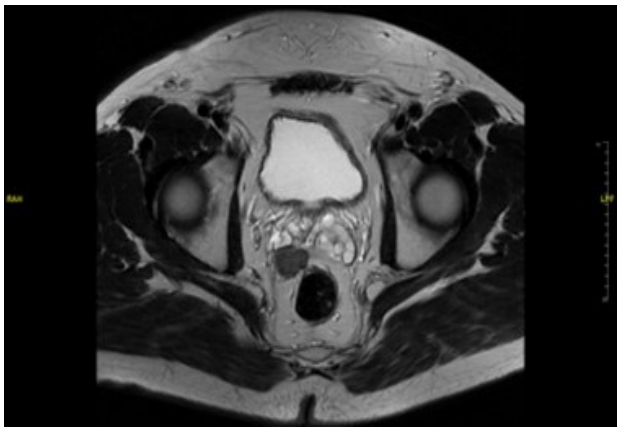

Figure 2. Axial T2-A MRI examination: Hypointense mass with smooth contours in the proper anterolateral aspect of the rectum.

A colonoscopy was performed to eliminate the possibility that the tumor was the second primary tumor originating from the rectum, and no endoluminal pathology was observed. No metastases were detected in other parts of the body, according to Gallium-68 PET/CT. The result of the needle biopsy was grade-2 NET. The patient's first surgery was performed by laparotomy, and the same incision line was used again and open laparotomy was performed. Perioperative frozen sections were performed, NET was confirmed, and the surgical margins were reported with clear margins. The patient was discharged on the 3rd postoperative day with a cisplatin and etoposide chemotherapy protocol planned. No active complaints or residual lesions were observed after chemotherapy in the first year of Follow-Up.

In the microscopic examination, it was observed that the tumor generally formed solid islands. Tumor cells show mild atypia and have round-oval nuclei with small, eccentrically located nucleoli. The nuclear chromatin structure has a fine granular chromatin distribution (Salt and Pepper Pattern) specific to NETs (Figure 3 a, b, and c).

Tumor cells were stained positively with CD56, synaptophysin, and chromogranin. KI-67 index was found to be 18%. With these findings, the case was diagnosed with grade 2/3 NET, showing moderate atypia. (Figure 4a, b, c, and d)

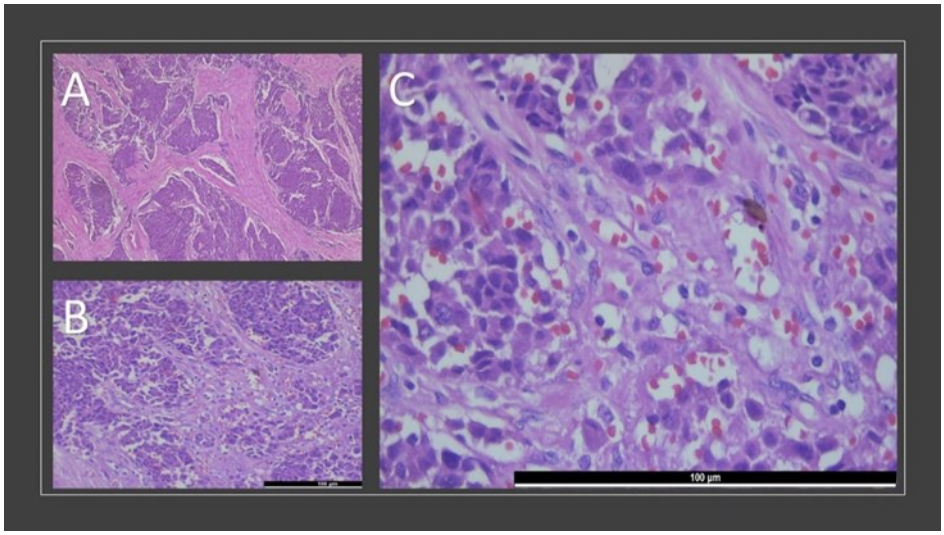

Figure 3. a: Solid tumor islands within desmoplastic stroma (Hematoxylin and Eosin X40); b: The cells forming the tumor show mild atypia and have a fine granular chromatin distribution (Hematoxylin and Eosin X200); c: A closer view of the tumor cells shows round-oval nuclei with small, eccentrically located nucleoli. The nuclear chromatin structure is observed in a Salt and Pepper Pattern (Hematoxylin and Eosin X400).

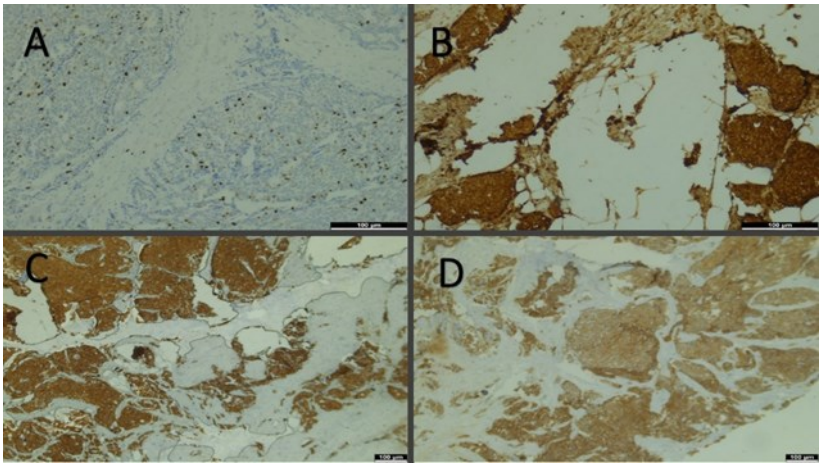

Figure 4. a: Brown positive staining with Ki 67 in 18% cell nuclei (X40); b: Brown positive staining with CD 56 (X40); c: Positive staining with synaptophysin (X100); d: Moderately positive staining with chromogranin (X40).

DISCUSSION AND CONCLUSION

Although appendiceal NETs are unlikely to metastasize, this possibility should always be considered. By a majority, NETs tend to metastasize to the liver. However, there is also the possibility of synchronous and metachronous colon cancer and other primary tumors.[9] Therefore, patients must undergo a colonoscopy and whole-body scanning with Gallium-68 PET/CT. Lymphovascular invasion can be considered a poor prognostic factor. Ki-67 index and grade are crucial and highly related to prognosis. In high-grade NET cases, complete resection and adjuvant chemotherapy can only increase overall survival.[5]

The grading system of NETs often involves assessing the histological appearance of the tumor cells and the Ki-67 proliferation index. There are three grades. Grade 1 (G1): Ki-67 index is usually less than 3%. Tumors with this grade tend to grow slowly and have a lower likelihood of aggressive behavior. Grade 2 (G2): Ki-67 index is between 3% and 20%. Tumors with this grade have an intermediate growth rate and behavior. Grade 3 (G3): Ki-67 index is more than 20%. Tumors with this grade tend to grow rapidly and have a higher potential for aggressive behavior and metastasis. In our case, the tumor was grade 2 due to the Ki 67 proliferation index being 18% and the presence of mild nuclear atypia.

Metastasis is influenced by factors such as tumor grade, size, location, and the presence of specific cellular markers. High-grade tumors, including high-grade appendix neuroendocrine tumors, are generally associated with a higher risk of metastasis due to their aggressive growth behavior.[5,6] It has also been found to be associated with tumor size and high-grade lymph node metastasis.[3,4] Conversely, it was shown that adverse outcome was significantly associated with tumor advanced stage, older age, and the presence of positive resection margins and extramural extension.[2] Particularly for NETs of pancreatic origin, the risk of recurrence is related to the Ki-67 ratio >10% and poorly differentiated pathological findings. Recurrences have been reported mainly in the pancreatic tissue, liver, and abdomen. However, specific recurrence sites for other NETs have not been frequently reported in the literature.[10] In this study, possible metastasis, even after a long time, may be related to the tumor's high grade, a size larger than 2 cm, and high Ki-67 proliferation index. The recurrent anatomical area is also remarkable.

In conclusion, the appearance of metastasis generally indicates that the tumor has progressed to an advanced stage. The treatment approach for metastatic neuroendocrine tumors often involves a combination of therapies, which may include surgery, targeted therapies, chemotherapy, and other interventions to manage symptoms and slow disease progression. A higher Ki-67 index generally indicates a higher rate of cell proliferation, which can suggest a more aggressive tumor behavior. However, each case is unique, and factors such as the tumor's characteristics, the patient's overall health, and other variables can influence the disease progression timeline.

Ethics Committee Approval: Ethics committee approval is not required. The patient/relatives have signed an informed consent/consent form, and the study was conducted following the international declaration, guidelines, etc.

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

Author Contributions: Concept-KG; Supervision-KG; Materials-KG, DD; Data Collection and/or Processing-KG, DD; Analysis and/or Interpretation-MU; Writing-KG, DD, MU.

Peer-review: Externally peer-reviewed.

Other Information: This case was presented orally at the 5th International Congress on Medical Sciences and Multidisciplinary Approaches Congress.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(3):277-282 *Online Türk Sağlık Bilimleri Dergisi 2024;9(3):277-282*

Short Bowel Syndrome: A Case Series and Review of Literature

Kısa Barsak Sendromu: Olgu Serisi ve Literatür Derlemesi

[1]Ali TAMER, [1]Tunahan ZENGİN

[1]Department of Internal Medicine, Sakarya University Faculty of Medicine, Sakarya, Tükiye

Ali Tamer: https://orcid.org/0000-0003-2005-0737
Tunahan Zengin: https://orcid.org/0009-0007-4335-8781

ABSTRACT
Short Bowel Syndrome, defined as remaining small bowel in continuity of less than 200 cm, is a disorder with varied presentations and frequent and often difficult-to-manage complications. The most commonly encountered complications are mainly nutritional, gastrointestinal and nephrological. Anticoagulation and bone disorders due to micronutrient and drug malabsorption, among other causes, are also encountered. The clinical follow-ups and considerations necessary vary between patients. Functional, pathophysiological, etiological, clinical and anatomical classifications exist to help physicians predict the required interventions. Herein, we summarise our experience with three cases with differing presentations and prognoses. We discuss the problems encountered during their management in light of the existing literature and guidelines. Specialised units and a multi-departmental approach remain vital in managing intestinal failure and short bowel syndrome; better tools and further research are yet to be required.
Keywords: Catheter-related infections, home parenteral nutrition, sepsis

ÖZ
İnce bağırsağın 200 cm'den daha az devamlılıkta kalması olarak tanımlanan Kısa Bağırsak Sendromu, çeşitli prezentasyonlara sahip, sık görülen ve sıklıkla tedavisi zor komplikasyonlarla seyreden bir hastalıktır. En sık karşılaşılan komplikasyonlar temel olarak beslenme, gastrointestinal ve nefrolojiktir. Diğer sebeplerin yanı sıra mikrobesin ve ilaç malabsorbsiyonuna bağlı antikoagülasyon ve kemik bozukluklarıyla da karşılaşılmaktadır. Klinik takipler ve gerekli hususlar hastalar arasında farklılık gösterir. Hekimlerin gerekli müdahaleleri tahmin etmelerine yardımcı olmak için fonksiyonel, patofizyolojik, etiyolojik, klinik ve anatomik sınıflandırmalar mevcuttur. Burada farklı sunum ve prognozlara sahip üç vakayla ilgili deneyimlerimizin bir özetini sunuyoruz. Yönetimi sırasında karşılaşılan sorunları mevcut literatür ve kılavuzlar ışığında tartışıyoruz. Bağırsak yetmezliği ve kısa bağırsak sendromu vakalarının tedavisinde özel birimler ve çok bölümlü yaklaşım hala hayati önem taşır ve daha iyi araçlara ve daha fazla araştırmaya ihtiyaç mevcuttur.
Anahtar Kelimeler: Evde parenteral besleme, kateter kaynaklı enfeksiyonlar, sepsis

Sorumlu Yazar / Corresponding Author:
Ali Tamer,
Sakarya University Faculty of Medicine, Department of Internal Medicine, Sakarya, Tükiye
Tel: +905335400368
E-mail: tamer@sakarya.edu.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 16/04/2024
Kabul Tarihi/ Accepted: 12/06/2024
Online Yayın Tarihi/ Published: 16/09/2024

Atıf / Cited: Tamer A and Zengin T. Short Bowel Syndrome: A Case Series and Review of Literature. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(3):277-282. doi: 10.26453/otjhs.1469381

INTRODUCTION

Intestinal failure (IF) is defined as gut function below the minimal amount necessary for absorption of macronutrients and/or electrolytes to the point of requiring intravenous intervention in order to continue health and growth. Intestinal insufficiency is defined as a gut function reduction that does not require any intravenous (IV) intervention for continued health and/or growth.[1]

The remaining small bowel in continuity of less than 200 cm is defined as short bowel syndrome (SBS). In adults, short bowel syndrome is usually caused by surgical resections due to Crohn's disease, malignancy, radiation or vascular insufficiency.[2]

IF is classified under five categories: functional classification (type 1 acute and short-term conditions, type 2 prolonged acute conditions, and type 3 potentially chronic conditions), pathophysiological classification (short bowel, intestinal fistula, intestinal dysmotility, mechanical obstruction, and extensive small bowel mucosal disease), etiological classification (severe GI or systemic benign diseases and end-stage intra-abdominal or pelvic cancer), clinical classification (based on requirements for energy and the volume of IV supplementation), anatomical classification (end-jejunostomy with no colon in continuity, jejunocolic anastomosis with no ileocecal valve and a part of the colon in continuity, and jejunoileal

anastomosis with both the ileocecal valve and the entire colon in continuity). Patients with irreversible IF will require long-term or lifelong home parenteral nutrition (HPN) or intestinal transplantation.[3]

In this presentation, we aimed to present 3 cases diagnosed with Short Bowel Syndrome that we followed up with three differing presentations and prognoses.

CASES

A signed informed consent in accordance with international guidelines was obtained from all cases presented herein.

CASE 1

A 46-year-old female patient was admitted to the emergency department 11 years ago with abdominal pain. After evaluation, she was diagnosed with mesenteric thrombosis and underwent a jejunostomy, leaving 50 cm of small intestine from the ligament of Treitz (subtotal small intestine resection + right hemicolectomy + Hartman procedure). For 11 years, she was followed and treated with HPN with Type 3 chronic intestinal insufficiency. The left half of the transverse colon, descending colon, and sigmoid colon are healthy but not functional. There was no feature in her medical history other than the use of oral contraceptives. No features have been identified in her family history and habits. No features other than jejunostomy were detected in her physical examination. The thrombophilia panel was evaluated as normal.

Adaptation Period: In the postoperative period, the patient was treated with oral fluid restriction of 1.5 litres, a short bowel diet, IV proton pump inhibitors, and IV glutamine. With Abound™ (Abbott) and Modulen™ (Nestle) treatments as an oral nutrition supplement, the jejunostomy discharge of 5 litres decreased to 2.5 litres. Olive oil-based parenteral nutrition treatment was started at 25 kcal/kg/day. The fluid deficit was met by calculating the jejunostomy discharge and the insensible loss. IV solutions were used for trace elements and vitamins.

Chronic Period: As home parenteral nutrition treatment, multi-chamber bag parenteral nutrition preparation, parenteral fluid and vitamin replacement are administered by the patient daily and infused overnight. Follow-ups are weekly. Upon admission postoperatively, the patient weighed 64 kg (BMI: 28.4). Still, weight loss developed, and she is being followed at 35 kg (BMI: 15.5). Clinical follow-up revealed that oral intake did not contribute to caloric intake. Vitamin C and selenium levels were low, while vitamin A, E, zinc, copper and chromium levels were normal.

Follow-up Process: She was hospitalised 68 times during the 11-year follow-up period. 45 hospitalisations were due to infectious reasons, and 23 were non-infectious.

Complication Management: She was admitted 41 times due to catheter infections (one of which was ICU), twice for upper respiratory infection, once for urinary tract infections and once for acute cholangitis. She was admitted twice for acute kidney injury, nine times for supportive treatment, twice for port care, once for hemoptysis, twice for anaemia, three times for elevated liver enzymes, once for suspected pulmonary embolism, once for cholecystitis, once for severe hyperkalemia, once for elevated CRP for a total of 23 non-infectious admissions. Hypokalemia and hypomagnesemia were the most commonly detected electrolyte imbalances. It was determined that she had disrupted her diet with hyperosmolar fluid (fruit juice). Spironolactone tablets were initiated to control hypokalemia, and her potassium levels stabilised around 3-3.5. Vitamin K deficiency developed two years after diagnosis. Despite no elevation of INR, excessive bleeding was noted during her catheter insertions. Three ampoules of vitamin K were replaced intravenously annually. No further bleeding complications occurred. In nephrological evaluation, although the patient presents with intermittent AKI, eGFR is 85 ml/min. In osteoporosis evaluation, femur T score – 2.5, lumbar vertebra – 2.8 was determined. Vitamin D supplements were administered IM.

CASE 2

A 54-year-old male patient was admitted to the emergency department seven years ago with abdominal pain and was diagnosed with portal and mesenteric vein thrombosis. He underwent subtotal small intestine and right colon resection, 50 cm from Treitz, and a jejuno-colic anastomosis (transverse colon) operation. He has been followed with enteral nutrition for seven years without the need for parenteral support treatment. His medical history includes hypertension and lower extremity superficial thrombophlebitis one year before the date of the event. No characteristics were noted in his family history and habits. On physical examination, there is no feature except a surgical scar in the abdomen. In the etiological evaluation, he was diagnosed with thrombophilia panel positivity (MTHFR gene mutation and PAI serpine 1 gene heterozygous mutation) and Behçet's disease (HLA B51 positive). Intestinal failure was considered as Type 3 chronic intestinal failure. Abdominal ultrasonography revealed portal vein thrombosis, an infarct area in the right posterior liver, and splenomegaly. The patient was initiated on methylprednisolone, azathioprine, warfarin and ramipril.

Adaptation Period: Nutritional therapy was arranged as short bowel diet regulation at 30 kcal/kg/

day, oral fluid restriction, oral vitamin supplement, oral proton pump inhibitor, and loperamide. However, the patient could not reach sufficient calories during daily nutritional monitoring. Therefore, Abound™, Modulen™, Fortimel Compact Protein™ and Fortimel Energy™ 1.5 kcal were started as oral nutrition products for the patient. The patient's weight loss was controlled with 40 kcal/kg/day treatment. The frequency of defecation became stable at thrice per day.

Chronic Period: The patient, who weighed 94 kg (BMI: 29.65) preoperatively, weighed 84 kg (BMI: 26.5) at the outpatient clinic follow-up. After seven years of follow-ups, his weight is currently 72 kg (BMI: 22.7).

Follow-up process*:* He was hospitalised twice for parenteral support treatment due to weight loss but was unsuccessful due to upper extremity brachial vein thrombosis in both hospitalisations. Vitamin B12 deficiency developed and was replaced intramuscularly following inadequate response to sublingual replacement. Vitamin D deficiency was replaced with IM. Oral vitamin and micronutrient support was given. For magnesium deficiency, oral magnesium preparations were used twice a day. Due to the anaemia, treatment with IV iron preparations was needed four times.

Complication Management: Gastrointestinal complications: The patient's diarrhea was followed at 3-4 times daily. Whenever the patient disrupted his diet, the complaints of dyspepsia, tenesmus and diarrhea increased. They were controlled with diet regulation, pancreatic enzyme and ursodeoxycholic acid. In the 6th month, gallbladder stones were detected and are being monitored without complications. His diet was revised due to calcium oxalate crystals in the urine. Regarding micronutrients, after six months of follow-up, vitamin B12 and vitamin D were found insufficient and were replaced with IM. After muscle cramps, magnesium deficiency was detected and controlled with oral magnesium twice daily. Iron deficiency developed and treated with IV iron therapy. Low levels of selenium, copper, vitamin C and vitamin A are treated with a multivitamin preparation containing oral trace elements twice daily. Under warfarin, half a tablet/day, the INR levels remained between 1.5 and 3.5. During this period, dose regulations were required. Once his INR level was detected above 10 and the patient presented with hematuria, it was managed with dose regulation without additional complications. Diet regulations and fibre changes within the nutritional products affect the patient's warfarin dose. In nephrological evaluation, eGFR is monitored at 105 ml/min. Intermittent laboratory findings of INR above 4 cause hematuria attacks and, alongside the concurrent calcium oxalate crystals, cause associated renal colic complaints. No stones were detected. No osteopenia was detected at osteoporosis follow-ups.

CASE 3

A 65-year-old female patient with a history of cholecystectomy, sleeve gastrectomy, previous tongue cancer (and radiotherapy), COPD, coronary artery disease, paroxysmal atrial fibrillation, pulmonary hypertension, and chronic renal failure presented three years ago with abdominal pain. She was admitted to the emergency clinic and, with the diagnosis of mesenteric ischemia, underwent small bowel resection, leaving 40 cm from Treitz, and a right hemicolectomy was performed, including the right half of the transverse colon. The patient was followed with parenteral nutrition for four months, then underwent STEP operation and jejunocolic anastomosis. She has been followed up with chronic intestinal failure for the last three years.

Adaptation Period: Following jejunostomy and right colon hemicolectomy surgery, she was followed with parenteral nutrition. For two months postoperatively, she was managed as an inpatient, with varying hyper-hypovolemia, IV proton pump inhibitors, oral fluid restriction, short bowel diet, and one catheter infection. STEP surgery was performed after two months. During the adaptation period after STEP surgery, oral proton pump inhibitors, ursodeoxycholic acid, and pancreatic enzymes were added to her treatment and were beneficial for her dyspeptic complaints. Due to radiotherapy, oral intake was impaired due to insufficient saliva secretion and lack of teeth. She could not tolerate glutamine, Abound™ and additional nutritional support products. Oral calories consumed ranged between 1500 kcal/day and 2200 kcal/day. The protein and calorie intake of the diet was increased. Since the patient had a sleeve gastrectomy in the past, bromelain was used for protein digestion to no benefit.

Chronic Period and Follow-Up Process: Home health care units monitored the patient at home. She was admitted intermittently for anaemia for approximately six weeks and once due to acute kidney injury. The need for parenteral nutrition remained very limited after STEP surgery, and the need for fluid and electrolyte support bi-weekly continued. Parenteral nutrition and IV vitamin support are needed for three days every 2-3 weeks.

A bone marrow biopsy was performed to examine the aetiology of anemia, and erythropoietin treatment was started upon detection of myelodysplasia. The patient no longer needs blood transfusions. The genetic thrombophilia panel was evaluated as normal.

Complication Management: Nephrologically, eGFR is monitored at 30 ml/min and Creatinine at 1.7 mg/dl. Gastrointestinal complications include com-

plaints of dyspepsia and diarrhea. Defecation is controlled at 3-4 times daily with proton pump inhibitors, pancreatic enzyme, ursodeoxycholic acid and diet management. Difficulty swallowing, absence of teeth, previous sleeve gastrectomy and cholecystectomy restrict oral calorie and fluid intake. She also experiences frequent hypervolemia-hypovolemia problems and hypo-hypertensive attacks due to cardiorenal problems. The patient, whose weight was 83 kg (BMI: 34.5) preoperatively and 69 kg (BMI: 28.8) postoperatively, is currently being followed at 61 kg (BMI: 25.4). Oral intake support is managed by dietary regulations and high protein liquid food intake. The patient doesn't consume nutritional products. Citrulline levels were normal. B12 deficiency is treated intramuscularly. Oral multivitamin tablets, folic acid, oral zinc and magnesium supplements are needed twice daily. During follow-ups, copper and selenium levels were low. The fluid requirement is 5 litres every 14 days and is provided peripherally with diuretic treatment. Potassium levels vary between 3-3.5. There is borderline hypophosphatemia (2,4). Albumin levels are monitored as 2.9 g/dl. Osteoporosis: During her follow-ups, osteoporosis was detected in 2020. IM Vitamin D replacement was initiated. IV osteoporosis treatment is planned.

DISCUSSION AND CONCLUSION

In adults, SBS is a special clinical condition that requires follow-up and treatment by units specialised in the management of nutrition and complications that develop after massive intestinal surgery. Management of nutritional therapy begins in the postoperative period and varies depending on the location and length of intestinal resection. This case series discusses the management of macronutrient and micronutrient deficiencies and their complications and medications.

The cases defined are Case 1; type 3, benign aetiology, end jejunostomy, clinically classified as PN1 and FE3, an adult case with no additional disease, Case 2; type 3, benign aetiology, jejunocolic anastomosis (no ileocecal valve), an adult case with known hypertension and Behçet's disease, Case 3; type 3, benign aetiology, STEP and jejunocolic anastomosis (no ileocecal valve), clinically classified as PN1 and FE1, adult and with previous diagnoses of tongue cancer (radiotherapy), hypertension, COPD, CKD, diastolic heart failure, paroxysmal atrial fibrillation, sleeve gastrectomy and cholecystectomy.

In the postoperative period, an intestinal rehabilitation program is needed to increase the function of the remaining intestine, minimise the need for parenteral nutrition and liquid electrolytes, and prevent complications. In this adaptation process (6 months-2 years), glutamine, enteral nutrition, modified diet, growth factors (GLP-2 agonist), growth hormone, octreotide, proton pump inhibitors and loperamide treatments have been used.[4] The ESPEN Guide evaluates these recommendations more clearly.[1] In all of our cases, a diet high in complex carbohydrates and protein and low in fat was recommended during the adaptation period. Fluid intake was restricted. Glutamine, PPI, loperamide, and polymeric products (primarily high in MCT) were used. A decrease in the number and amount of defecation (including stoma exit) was achieved in all cases. Enteral supplement products with high MCT content couldn't be continued long-term due to intolerance and were continued with polymeric products. Although dietary compliance deteriorated in the long term, the number of defecations did not increase.

For the nutritional treatment of cases with short bowel syndrome, enteral and parenteral nutrition, liquid electrolyte replacement, and vitamin and trace element replacement needs should be evaluated and planned according to the patient's short bowel classifications.[5] While case 1 was followed up with an olive oil-based parenteral nutrition product, IV vitamins and liquid electrolyte replacement due to jejunostomy, case 2 was followed up with enteral nutrition. Polymeric products that prevent weight loss were used. Although Case 3 had STEP surgery, oral intake could not be increased above 2000 kcal/day, and enteral nutrition supplements could not be used due to the possible absence of a salivary gland, lack of teeth, and sleeve gastrectomy. Case 3 is followed up with an olive oil-based parenteral product for 3 days every 3 weeks. In patients with SBS, fat-soluble vitamin deficiencies (A, D, E and K), water-soluble vitamin deficiencies, vitamin B12, zinc, copper, selenium and iron deficiencies should be expected depending on the location and length of bowel resection. Clinical signs and laboratory findings of these deficiencies should be monitored.[6] In Case 1, micronutrient needs were replaced daily. Vitamin D was replaced IM. Three ampoules of vitamin K were replaced IV annually, although the INR was not prolonged (bleeding complications). Multivitamin and multimineral preparations are given once daily in case 2 and twice daily in case 3. However, vitamin D and B12 needed IM supplementation, and iron deficiency was replaced with IV.

In patients with SBS, fluid volume abnormality appears as hypovolemia or hypervolemia. Chronic dehydration, which is frequently encountered, can cause fatigue, nephrolithiasis, acute kidney injury, and chronic kidney disease. Oral and IV fluid intake, urine amount, stoma output amount and, if any, stool amount, urine Na, kidney function tests and weight should be monitored. Oral rehydration fluids can be used during the adaptation period. Hypertonic or hypotonic oral fluid intake should be avoided. Pa-

tients may need additional interventions such as periodic or daily PN or intravenous (IV) fluids, depending on the extent of bowel resection and the presence of a stoma.[6] A target of 1000-1200 ml/day urine output should be frequently recommended. In Case 1, fluid needs were replaced parenterally. There was no hydration problem in Case 2. In Case 3, hypervolemia was frequently encountered due to CHF and CKD. Diuretic treatment was initiated and was adjusted with proBNP monitoring.

In patients with Short Bowel Syndrome and intestinal motility disorder, the location and length of intestinal resection affect drug absorption. In addition, colon microbiota is necessary for vitamin K synthesis. Warfarin is absorbed in the stomach and proximal small intestine. Intestinal motility disorder, changes in colon microbiota, and vitamin K replacement, especially in patients receiving HPN, may pose difficulties in warfarin treatment.[7] This has led to the choice of direct-acting anticoagulant treatment (rivoraxaban). Case 2 is followed with half a warfarin tablet daily. The patient presents with intermittent hematuria and renal colic attacks. Case 3 is followed without complications with apixaban. Bone metabolism changes, and osteoporosis occurs in patients with SBS due to fatty tissue change, decrease in hormones produced from the intestine (GLP1, GLP2, GIP, glucagon, disruption of the intestine-bone axis), vitamin D and K malabsorption, calcium and magnesium malabsorption, kidney and liver damage.[8] In Case 1, osteopenia developed in the 5th year of follow-up and osteoporosis in the 10th year. Vitamin D support was provided. Osteopenia wasn't detected in Case 2. In Case 3, the patient was osteoporotic preoperatively and is receiving vitamin D supplementation.

In patients with SBS, parenteral nutrition complications such as sepsis, fatty liver after blood transfusions, steatohepatitis, liver failure, cholestasis, and gallstones may be encountered.[9] In Case 1, early-period liver enzyme elevation improved when daily vitamin administration was discontinued. In Case 2, elevated liver enzymes were considered to be caused by overfeeding and parenteral nutrition was discontinued. Instead of a multi-chamber bag, the lipid was cut, and amino acid and glucose solutions were administered. Following this, the liver enzymes regressed. Liver enzyme elevation developed when parenteral nutrition calories were given according to the patient's original weight to increase weight after weight loss. During another liver enzyme elevation in Case 1, a cholecystitis-cholangitis attack was considered and was intervened with ERCP. Since the patient's liver enzyme levels remained stable and slight hyperbilirubinemia continued, ursodeoxycholic acid was initiated and was beneficial. Case 2 also developed gallstones but is still being monitored without complications. He is being monitored with moderate elevation of liver enzymes due to liver infarction. Case 3 cholecystectomy was performed before short bowel disease. She is being monitored without liver enzyme elevation. In gastrointestinal complaints, cases 2 and 3 in gastrointestinal complaints benefited from PPI, a pancreatic enzyme, loperamide and ursodeoxycholic acid treatments for dyspepsia, diarrhea and tenesmus. Acute kidney injury, chronic renal failure, calcium oxalate stones and recurrent urinary infections are the nephrological problems encountered, especially in patients with intact colon, especially for the latter two.[6] Diet and fluid-electrolyte balance and prevention of recurrent infections are recommended to prevent the development of kidney damage. Recurrent AKI was encountered in Case 1. In case 2, calcium oxalate crystals and renal colic attacks are observed, and in case 3, CKD is observed. HPN therapy is a vital treatment for some patients with short bowel syndrome. However, catheter-related bloodstream infections are associated with life-threatening complications, especially sepsis, septic shock, and metastatic infections.[10] In Case 1, catheter infection was a frequent and life-threatening problem.

In conclusion, short bowel syndrome requires nutritional therapy and multidisciplinary management of infectious, renal, hepatobiliary and bone metabolism complications caused by disease and nutrition. Advanced age, the presence of an underlying chronic disease and follow-up procedures also affect the patient's clinical morbidity and mortality.

Ethics Committee Approval: The patients have signed an informed consent form, and the study was conducted following international guidelines.

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

Author Contributions: Concept – AT; Supervision – AT; Data Collection and Processing – AT; Analysis and Interpretation – AT, TZ; Writing –AT, TZ.

Peer-review: Externally peer-reviewed.

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