ISSN: 1305-9319 e-ISSN: 1305-9327 Number: 2 Volume: 21 Year: 2025

MEDICAL JOURNAL OF BAKIRKÖY

www.bakirkoytip.org

ISSN: 1305-9319 e-ISSN: 1305-9327 Number: 2 Volume: 21 Year: 2025

MEDICAL JOURNAL OF BAKIRKÖY

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

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

Please refer to the journal's webpage **(https://bakirkoymedj.org/)** for "Ethical Policy" and "Instructions to Authors".

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Tel: +90 212 414 71 59 / 90 212 241 68 20
mail: info@bakirkoytip.org

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

Printing Date: June 2025
ISSN: 1305-9319 **E-ISSN:** 1305-9327
International scientific journal published quarterly.

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University of Health Sciences Türkiye, Adana City Training and Research Hospital, Clinic of Urology, Adana, Türkiye

• **Prof. MD. Zahide Mine Yazıcı**
University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Otorhinolaryngology, Istanbul, Türkiye

• **Prof. MD. Zeynel Abidin Öztürk**
Gaziantep University Şahinbey Research and Practice Hospital, Clinic of Geriatrics, Gaziantep, Türkiye

• **Assoc. Prof. MD. Zeynep Çizmeci**
University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Microbiology, Istanbul, Türkiye

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):127-133
DOI: 10.4274/BMJ.galenos.2025.2024.7-6

Research

Relationship Between Non-diagnostic Result and Nodule Size in Thyroid Fine Needle Aspiration Biopsies

Tiroid İnce İğne Aspirasyon Biyopsilerinde Non-diagnostik Tanı ile Nodül Boyutları Arasındaki İlişki

Betül Öndeş Denizli[1], Özlem Polat[1], Fatmagül Kuşku Çabuk[2], Erdinç Denizli[3], Medine Şişman[1], Hilal Yönet Arslan[1], Hamide Pişkinpaşa[4], Meral Mert[4]

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

[2]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pathology, İstanbul, Türkiye

[3]University of Health Sciences Türkiye, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Türkiye

[4]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Endocrinology and Metabolism, İstanbul, Türkiye

ABSTRACT

Objective: Twenty-one percent of total thyroid fine needle aspiration biopsies (FNABs) result non-diagnostic (ND). It is a major problem in management of thyroid nodules. The aim of this study is to investigate the relationship among ND result, nodule size, ultrasonographic features and laboratory findings in patients whose cytopathologic examination of thyroid FNABs resulted in ND.

Methods: Retrospectively, 520 patients aged 18-85 years, whose thyroid FNABs were performed between the years 2012-2016 and whose cytopathology was ND, were evaluated with laboratory, ultrasonography, and final pathologic results.

Results: There was no significant relationship among ND result, nodule size, and final pathology result. It was determined that no macrocalcifications were found in any of the ultrasonographic examinations of the nodules evaluated to be pathologically malignant. There was a significant relationship between the free triiodothyronine (fT_3) level and the total number of biopsies taken from the same nodule. Significant relationship was observed between the anti-thyroid peroxidase (anti-TPO) level and the number of biopsies taken, which resulted in ND. In patients with high anti-TPO levels, an ND biopsy is one of the follow-up biopsies taken from the nodule.

Conclusion: We concluded there is no distinct correlation between the ND result and nodule dimensions in the FNAB. Ultrasonographic features still cannot provide a prediction of whether the nodule is benign or malignant. Laboratory findings like fT_3 and anti-TPO, may provide guidance to the clinical approach.

Keywords: Nodule size, non-diagnostic, thyroid fine needle aspiration biopsy, ultrasonographic characteristics

ÖZ

Amaç: Toplam tiroid ince iğne aspirasyon biyopsisinin (İİAB) yüzde 21'i sonucu non-diagnostiktir (ND). Bu, tiroid nodüllerinin tedavisinde önemli bir sorundur. Bu çalışmanın amacı tiroid İİAB sitopatolojik incelemesi ND olan hastalarda ND sonuç, nodül boyutu, ultrasonografik (USG) özellikler ve laboratuvar bulguları arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: 2012-2016 yılları arasında tiroid İİAB'si yapılan ve sitopatolojisi ND 18-85 yaş arası 520 hasta retrospektif olarak laboratuvar, USG ve patoloji sonuçlarıyla değerlendirildi.

Bulgular: ND sonuç, nodül boyutu ve nihai patoloji sonucu arasında anlamlı bir ilişki yoktu. Patolojik olarak malign olarak değerlendirilen nodüllerin USG incelemelerinin hiçbirinde makrokalsifikasyona rastlanmadığı belirlendi. Serbest triiyodotironin (fT3) düzeyi ile aynı nodülden alınan toplam biyopsi sayısı arasında da anlamlı bir ilişki vardı. Ayrıca ND olarak değerlendirilen biyopsinin, hastanın bu nodülünden alınan kaçıncı biyopsisi olduğu ile anti-tiroid peroksidaz (anti-TPO) değeri arasında anlamlı ilişki görülmektedir. Anti-TPO değeri yüksek olan hastalarda ND çıkan biyopsinin, hastanın bu nodülünden alınan daha sonraki biyopsilerinden biri olduğu görülmektedir.

Address for Correspondence: Betül Öndeş Denizli MD, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Family Medicine, İstanbul, Türkiye
E-mail: betulondes@gmail.com **ORCID ID:** orcid.org/0000-0002-0603-6288

Cite as: Öndeş Denizli B, Polat Ö, Kuşku Çabuk F, Denizli E, Şişman M, Yönet Arslan H, et al. Relationship between non-diagnostic result and nodule size in thyroid fine needle aspiration biopsies. Med J Bakirkoy. 2025;21(2):127-133

Received: 19.07.2024
Accepted: 27.01.2025
Publication Date: 04.06.2025

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ÖZ

Sonuç: ND sonuç ile İİAB'deki nodül boyutları arasında belirgin bir korelasyon olmadığı sonucuna vardık. USG özellikleri hala nodülün benign mi malign mi olduğuna dair kesin bir tahmin sağlayamamaktadır. fT3 ve anti-TPO gibi laboratuvar bulguları, klinik yaklaşımda yol gösterici olabilir.

Anahtar Kelimeler: Nodül boyutu, non-diagnostik, tiroid ince iğne aspirasyon biyopsisi, ultrasonografik özellikler

INTRODUCTION

Approximately 60% of adults have thyroid nodules detected by ultrasound, but most are clinically insignificant. Thyroid nodules are more common in women than in men and in areas where iodine intake is limited. The frequency of nodules increases with age, and the vast majority, 95%, are benign (1).

Ultrasonography and fine needle aspiration are of great importance in the diagnosis and follow-up of thyroid nodules. Clinicians, surgeons, pathologists, and oncologists work together in the management of thyroid nodules. There was a need for standardization of the cytopathological examination of thyroid aspiration sampling using a common language to increase the sensitivity and specificity of sampling in managing the patient's thyroid disease.

This problem was largely resolved with the "Bethesda Thyroid Cytopathology Reporting System" (TBSRTC). Compared to previous systems, TBSRTC has allowed for a significant reduction in the rate of ND/undetermined cases, making the results of fine needle aspiration biopsies (FNABs) more clinically useful. TBSRTC improves communication between cytopathologists, reduces the number of unnecessary operations in benign lesions, and makes it possible to perform timely surgical interventions and predict the risk of thyroid cancer in patients with malignant lesions. It provides simple and reliable data exchange not only among various laboratories, but also institutions all around the world (2).

There are classifications based on nodule size and ultrasonographic (USG) features, such as the American College of Radiology Thyroid Imaging Reporting and Data System and the American Thyroid Association (ATA) guide. In recent years, studies have been carried out on AI-based classification.

Additionally, molecular testing has emerged as a powerful tool with the potential to improve diagnostic evaluation of indeterminate nodules preoperatively (3).

FNAB has an indispensable role in revealing the risk of malignancy, even though it is possible to obtain valuable findings about the thyroid nodule non-invasively with detailed USG examination and laboratory findings. However, due to the insufficiency of the material or the incompatibility of the sample taken during the biopsy, non-diagnostic (ND) pathology samples constitute a dilemma in the clinical approach (4).

Our goal in this study was to investigate the relationship among ND result, nodule size, USG features and laboratory findings in patients who had cytopathologic examination of thyroid FNABs resulting in ND.

METHODS

After obtaining the approval of the Ethics Committee of University of Health Sciences of Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2017-01-02, date: 17.04.2017), the reports of 12,219 patients who underwent pathological examination from the archive files between 2012 and 2016 were reviewed. As the study had a retrospective design, informed consent was not required from the patients. The patients were divided into two groups based on findings from thyroid FNAB (n=10,718) and thyroidectomy specimens (n=1,501). Afterwards, the results of FNAB of 10,718 patients were investigated, and it revealed that the pathology reports of 838 patients were evaluated as ND. USG reports of the patients evaluated as ND were obtained from hospital archives. 318 patients, whose USG results could not be obtained from the archives, were excluded from the study as planned. The study was performed on 520 patients between the ages of 18 and 85 who were evaluated as ND as a result of FNAB. Their USG results were obtained from the archives (Figure 1).

The records of these patients were evaluated retrospectively. The final pathology diagnoses, based on the nodule size and USG features, if any, were established from biopsies made from this nodule. In addition to the demographic information of the patients, in terms of USG features, the length of the nodule in 2 dimensions, whether the nodule was cystic or solitary, whether it was calcified, border irregularity, vascularization, whether it gave a halo, and echogenicity features were examined.

As laboratory analysis; serum thyroid stimulating hormone (TSH), free triiodothyronine (fT_3), free tetraiodothyronine (fT_4), anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) levels were screened.

Statistical Analysis

Normality tests were performed for each variable considered in the study, and Kolmogorov-Smirnov and Shapiro-Wilk tests were applied. Since the variables had $p<0.05$, it was determined that they were not normally distributed and non-parametric methods were preferred in the analysis. The data considered have both categorical and continuous data structures. Chi-square analysis was used to determine the relationship between two categorical variables, and Kendall's tau-b correlation coefficient was used to analyze two continuous variables. In the analysis of group differences, the Mann-Whitney U test was applied for two groups and the Kruskal-Wallis test was applied for three or more groups. Since the normal distribution is not used to describe the statistics, median and range (minimum-maximum) values are given for continuous data. Frequency distribution tables were interpreted for categorical data. Analyses were made with SPSS version 22.0, and significance was evaluated at $p<0.01$ and $p<0.05$ levels.

RESULTS

In our study, all patients aged between 18-85 years who were evaluated as ND as a result of FNAB performed in our hospital between 2012 and 2016 and whose USG results could be obtained from hospital archives were included. There were 520 patients who met these criteria.

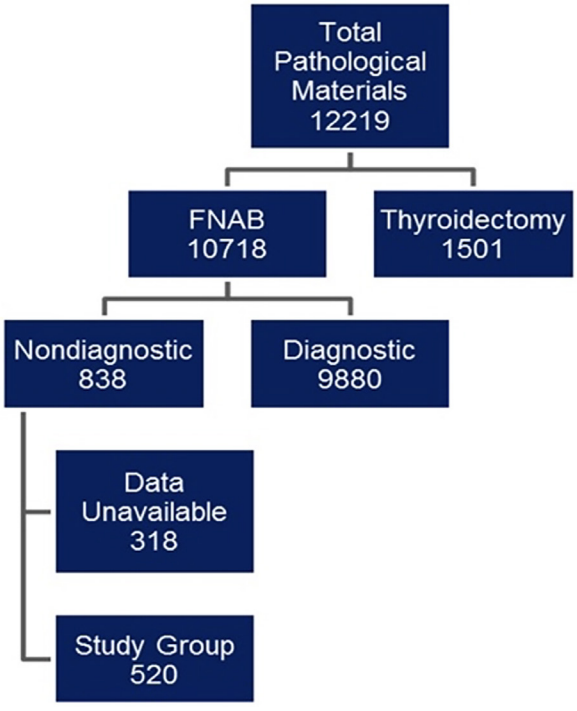


Figure 1. The distribution of the ND patient group in all examinations. FNAB: Fine needle aspiration biopsie, ND: Non-diagnostic

85.2% of all patients (n=443) were women, 14.8% (n=77) were men, and the average age was 52 years.

In the 2-dimensional evaluation of the nodule diameters, the larger 1st diameter was found to be 15 mm on average, and the smaller 2nd diameter was 10 mm.

Upon inspection of the largest first diameter of nodule sizes in patients, 16.5% (n=86) had nodules between 1-10 mm, 47.9% (n=249) between 11-20 mm, 19.8% (n=103) between 21-30 mm, 9.8% (n=51) between 31-40 mm, and 6% (n=31) had nodules greater than 40 mm.

When inspecting the smaller 2nd diameter of the nodule size of patients, 43.7% (n=227) is between 1-10 mm, 41.5% (n=216) is between 11-20 mm, 11.3% (n=59) is between 21-30 mm, 2.3% (n=12) is between 31-40 mm, and 1.2% (n=6) is greater than 40 mm.

When the USG properties of the biopsies were evaluated in terms of the presence of cystic components, it was observed that there was an approximately equal distribution. Microcalcification was detected in 15.8% (n: 82) of the patients and macrocalcification in 10.6% (n=55). It was observed that only 1.7% of the patients (n=9) had vascularity. Borders were regular in 91% (n=473) of the nodules taken, and in 9% (n=47), borders were irregular. The presence of halo around the nodule was observed in 25.6% (n=133) of all patients. A classification of nodules according to their echogenicity revealed that 37.9% (n=197) are hypoechogenic, 25.2% (n=131) hypo-isoechogenic, 28.1% (n=146) isoechogenic, 3.1% (n=16) iso-hyperechogenic, 3.8% (n=20) hyperechogenic, and 1.9% (n=10) of them are mixed. 31.2% of 520 biopsies were reported as ND due to material insufficiency.

The median value for serum TSH level was 1.09, the minimum value was 0.01, and the maximum value was 76.12. Serum TSH levels were high in 11% of patients (n=57), low in 13.8% (n=72), and within the normal range in 75.2% (n=391) [normal values (N)=0.27-4.2 mIU/mL].

For the fT_3 level, the median value was 2.91, the minimum value 0.41, and the maximum value 6.84. Serum fT_3 level was found to be high in 18.5% (n=96) patients, low in 3.65% (n=19), and in 77.9% (n=405) was within normal limits (N=2-4.4 pg/mL).

The median value for the fT_4 level was 0.98, the minimum value 0.05, and the maximum value 9.03. Serum fT_4 level was found to be high in 2.31% (n=12), low in 30.8% (n=160), and within normal limits in 66.9% (n=348) of patients (N=0.93-1.7 ng/dL).

In serum anti-TPO level measurements, the median value was 13.23, the minimum value 1.45, and the maximum value

3,000. Serum anti-TPO levels were within normal limits (0-40 IU/mL) in 79.81% (n=415) of patients, while they were high in 20.19% (n=105).

The median value for serum anti-Tg level was 20, the minimum value was 10, and the maximum value was 3,000. Serum anti-Tg levels were found to be within normal limits in 79.23% (n=412) of patients, while they were high in 20.77% (n=108) (N=0-35 IU/mL).

While the total number of FNABs performed in the nodules diagnosed with ND was investigated in the study, 51.9% (n=270) of the patients had no other biopsy. 40.8% (n=212) had a total of 2 biopsies; 4.8% (n=25) had a total of 3 biopsies; 2.3% (n=12) had a total of 4 biopsies; and 2% (n=1) had a total of 5 biopsies.

When the group of 250 patients, excluding the 270 patients without any other biopsy, was examined, the number of ND results obtained from FNAB biopsies were as follows: 1st biopsy resulting in ND; 40.2% (n=209) were 1st biopsies resulting in ND 7.5% (n=39) were 2nd biopsy; 2nd 0.2% (n=1) were 3rd biopsies; 3rd 0.2% (n=1) were 4th biopsies.

Of 250 patients who underwent repeat biopsy, 24.4% (61 patients) were ND again, 70.8% (177 patients) were diagnosed as Bethesda 2, 1.6% (4 patients) as Bethesda 3, 0.8% (2 patients) as Bethesda 4, 1.2% (3 patients) as Bethesda 5, and 1.2% (3 patients) as Bethesda 6 (Table 1).

In the group of 250 patients whose final Bethesda results were obtained from the archives, there was no significant relationship between the large diameter or the small diameter values of the nodule diameter sizes and the Bethesda result (p>0.05) (Table 2).

It was concluded that there was no statistically significant difference between the nodule sizes and the number of biopsies taken that resulted in ND in the same group of 250 patients (p>0.05) (Table 3).

In the comparison made in terms of TSH levels in the group of 250 patients whose final Bethesda results were obtained from the archives, further analysis revealed significant trends. There was a significant difference between the nodule diameters, including large and small diameter values, and the presence of cystic components. While patients with low TSH levels had the largest diameters, patients with high TSH levels had the smallest diameters. the cystic component was statistically significantly more common in patients with low TSH levels and was observed less commonly in those with high TSH levels.

When the population of 250 patients whose final Bethesda results were obtained was analyzed according to the level of fT_3, it was seen that the FNAB performed with the same nodule was mostly applied in patients with high fT_3 level, and least in patients with normal fT_3 level (p<0.05) (Table 4). In other features, there was no statistically significant difference among groups.

In our study, patients were divided into two groups, normal and high, in terms of anti-TPO levels. A significant

Table 1. Distribution of final Bethesda results after repeat biopsies

	N	Percentage
Bethesda 1	61	24.4%
Bethesda 2	177	70.8%
Bethesda 3	4	1.6%
Bethesda 4	2	0.8%
Bethesda 5	3	1.2%
Bethesda 6	3	1.2%
Total	250	100%

Table 2. Bethesda results by nodule dimensions

	Result	N	Average rank	p-value
Nodule size greater diameter	Bethesda 1	61	127.86	0.432
	Bethesda 2	177	124.05	
	Bethesda 3	4	98.63	
	Bethesda 4	2	223.75	
	Bethesda 5	3	109.33	
	Bethesda 6	3	149.67	
	Total	250		
Nodule size smaller diameter	Bethesda 1	61	128.16	0.327
	Bethesda 2	177	123.81	
	Bethesda 3	4	106.13	
	Bethesda 4	2	233.25	
	Bethesda 5	3	97.67	
	Bethesda 6	3	152.67	
	Total	250		

Kruskal-Wallis test was used as statistical method

Table 3. Relationship of nodule diameters with ND FNAB

	Which FNAB resulted ND	N	Average rank	p-value
Nodule size greater diameter	1. Biopsy	209	123.97	0.446
	2. Biopsy	39	132.32	
	3. Biopsy	1	223.50	
	4. Biopsy	1	80.50	
Nodule size smaller diameter	1. Biopsy	209	124.95	0.298
	2. Biopsy	39	127.95	
	3. Biopsy	1	232.00	
	4. Biopsy	1	38.50	

Kruskal-Wallis test was used as statistical method
FNAB: Fine needle aspiration biopsie, ND: Non-diagnostic

relationship was observed between anti-TPO level and the biopsy number resulting in ND ($p<0.05$) (Table 5). In patients with high anti-TPO levels, the ND biopsy appears to be one of the subsequent biopsies taken from the nodule. Although there was no significant difference in the total number of biopsies performed or the final Bethesda results ($p>0.05$), further analysis is needed to understand the underlying factors.

DISCUSSION

Woo et al. (5) reported that in their study group of 1,203 patients, 84 patients (6.98%) had ND cytological results. In our study, 7.82% (n=838 patients) of 10,718 FNABs performed within a 5-year period were evaluated as ND.

Ziemianska et al. (6), reported that they examined 159 ND nodules and found a 20.8% ND result in repeated FNAB. In our study, ND results were obtained in 61 (24.4%) of 250 patients with repeated FNAB.

In the study of Glynn et al. (7) investigating 413 nodules, it was observed that 89% of the patients were women, the average age of the patients was, and the nodule diameter was 25 mm. In our study where ND nodules were examined, it was noteworthy that 85% of the patients were women, the average age of the patients was 52, and the average largest diameter of the nodules was 15. In our study, we evaluated only ND nodules; but Glynn et al. (7) included all nodules in their study; their nodule median size was 25 mm, while our median size was 15 mm. This suggesting that biopsy of smaller nodules probably results in increased ND results.

In one of the studies, on the relationship between nodule depth and ND diagnosis, nodule size was also investigated. Asakly et al. (8) have reported in their study, no significant relationship was found between nodule size and ND result. Xia et al. (9) reported nodule diameters between 5 and 10 mm that have macrocalcification were more likely to be ND in cytological results compared to those with a maximum diameter greater than 10 mm. This suggests that small nodules may be more likely to result in ND. Another study showed that nodules 1 cm or less were associated with ND and Bethesda system categories that are suspicious for malignancy compared to nodules greater than 1 cm (10). The reason for this association may be the difficulty of performing FNAB on small nodules.

Eun et al. (11) worked with nodules that had ND results after a second FNABs. Malignancy rates, patient characteristics, and USG features were compared in 297 nodules with an average patient age of 52 and an average diameter of 9.8 mm. The tumors were classified as benign or malignant through surgical resection or repeated FNAB. One hundred fifty-three patients were evaluated as benign based on a repeat biopsy result. In the 12-month follow-up, the nodules

Table 4. Relationship of fT_3 with ND FNAB

	fT_3 level	N	Average rank	Kruskal-Wallis test	p-value
ND FNAB biopsy number*	Low	47	129.17	1.866	0.393
	Normal	193	123.74		
	High	10	142.2		
Total number of FNABs taken	Low	47	136.6	6.194	0.035
	Normal	193	121.75		
	High	10	145.75		

*: Number of biopsy taken (1st biopsy, 2nd biopsy, 3rd biopsy, etc.) which resulted ND
Kruskal-Wallis test was used as statistical method
FNAB: Fine needle aspiration biopsie, ND: Non-diagnostic

Table 5. Relationship of anti-TPO with ND FNAB

	Anti-TPO level	N	Average rank	Kruskal-Wallis' test	p-value
Total Number of FNABs taken	Low	207	123.51	4.038	0.126
	Normal	43	135.07		
	High	250			
ND FNAB biopsy number*	Low	207	121.87	3.966	0.007
	Normal	43	142.98		
	High	250			

*: Number of biopsy taken (1st biopsy, 2nd biopsy, 3rd biopsy etc.) which resulted ND
Kruskal-Wallis test was used as statistical method
FNAB: Fine needle aspiration biopsie, ND: Non-diagnostic, anti-TPO: Anti-thyroid peroxidase

of 7 patients shrank; no change was observed in the nodules of 74 patients, and therefore, they were evaluated as benign; 63 patients were subsequently operated on. Of 297 ND nodules, 44 (14.8%) were evaluated as malignant, and 253 (85.2%) nodules were benign. In our study, ND results were obtained in 7.8% of all FNABs and unfortunately 24.4% of these FNABs were ND again. The mean diameter of these ND nodules was 18.6 mm. In the follow-up, while the benign cytology rate was 70.8% in cytopathological results, the control FNAB results for Bethesda categories 3, 4, 5, and 6 among 250 patients were 1.6%, 0.8%, 1.2%, and 1.2% respectively, with a total of 4.8%.

Recurrent ND FNABs have high ND rates and malignancy rates. Surgical resection, follow-up by USG, or the decision to repeat FNAB poses an important challenge in clinical management for clinicians and radiologists. There are up-to-date guidelines and management recommendations on this subject. In the ATA guideline, the risk of malignancy group is determined according to cutoff values for nodule sizes and USG features. In addition, the risk of malignancy in completely cystic nodules is evaluated as less than 1% and biopsy is not recommended (12). Yoon et al. (13) state that it is more appropriate to follow up nodules that have no suspicious USG findings especially completely cystic nodules. Eun et al. (11) also stated in their study that no tumor with more than 50% cystic sections was malignant. In our study, macrocalcification, which is one of the findings suggesting that the nodule is benign, was not observed in any of our 12 patients, all of whom were classified as Bethesda 3, 4, 5, or 6.

Woo et al. (5) also stated that the detection of hypoechogenicity in USG findings in recurrent ND FNABs was identified as a significant risk for malignancy. Kim et al. (14) classified nodules containing at least one of the USG features: microcalcification, irregular or microlobular nodule boundaries, pronounced hypoechogenicity, and a longer-than-width sign as positive. They classified nodules without any of these features as negative. Malignancy was detected in 46 of 82 positive nodules and only in 3 of 73 negative nodules. According to these numbers, sensitivity was calculated as 93.8%, specificity as 56.1%, positive predictive value as 56.1%, negative predictive value as 95.9%, and accuracy as 74.8%. In our study, the feature of nodules being longer than wide in the USG image was not collected; therefore, after excluding this feature and continuing with the classification, malignancy was detected in 9 of our 196 positive nodules and only 3 of 54 negative nodules. In our study, the negative predictive value was similarly 94%.

Woo et al. (5) stated that 51 patients who had ND results, in the second FNAB in a 1,203 patient study group, had 36 (70.6%) malignant nodules. Nodule diameter, hypoechogenicity, and microcalcification were important risks for malignancy. In the detailed examination, it was concluded that only hypoechogenicity is an independent risk factor for the ND result. In a study conducted by Çetin (15), an endocrinologist examined FNABs performed by 1 year, and investigated the factors affecting the ND result. It was determined that only hypoechogenicity increased the probability of an ND result (15). In our study, when both malignant and benign USG findings were examined in relation to ND results and Bethesda results, no statistically significant relationship was found.

In our study, when the patients were divided into three groups low, normal, and high according to TSH values, no significant differences were found in the number of FNABs performed on the patient's ND nodule, the number of biopsies obtained from the ND nodule, and the final Bethesda results. However, the differences in TSH levels are observed especially between ND nodules containing a cystic component and ND nodule sizes. Larger nodules are seen in patients with low TSH levels and smaller nodules in patients with higher TSH levels.

When the patients were divided into 3 groups as low, normal, and high according to fT_3 level, no significant difference was found between the number of FNABs performed on the patients' ND nodule and the final Bethesda result. However, the only relationship was observed between the fT_3 level and the total number of FNABs performed on the patient's ND nodule. It is seen that the number of FNABs applied to the patient is the highest with high fT_3 levels, while the lowest in normal fT_3 levels. Although the synchronicity of hyperthyroidism and malignancy is rare, there are many studies demonstrating this association (16-20). As this association becomes more known, more FNABs are being performed in patients with hyperthyroidism due to the risk of thyroid malignancy.

Current studies are being conducted on the management of thyroid nodules using AI. The most important report from research conducted in recent years is that the evaluation of AI can be successfully used as a computer-aided diagnosis system to assist clinicians in making further diagnostic and treatment decisions (21-23).

CONCLUSION

We concluded there is no distinct correlation between the ND result and nodule dimensions in the FNAB. Even

if some USG findings (macrocalcification and completely cystic nodules tend to be more likely benign but irregular bordered, hypoechogenic and microcalcified nodules more likely malignant) can assist clinicians in determining the malignancy risk of ND nodules, USG features still cannot provide a definitive prediction of whether the nodule is benign or malignant. As studies show the association of hyperthyroidism and thyroid malignancies, laboratory findings like fT_3 and anti-TPO, can provide guidance to the clinical approach in making decisions for follow-up, possible biopsy repeat or surgical resection.

ETHICS

Ethics Committee Approval: Approval was obtained from the Ethics Committee of University of Health Sciences of Türkiye, Bakırköy Sadi Konuk Training and Research Hospital (approval no: 2017-01-02, date: 17.04.2017).

Informed Consent: As the study had a retrospective design, informed consent was not required from the patients.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: Ö.P., F.K.Ç., H.P., M.M., Concept: B.Ö.D., Ö.P., M.Ş., H.Y.A., M.M., Design: B.Ö.D., E.D., H.P., M.M., Data Collection or Processing: B.Ö.D., F.K.Ç., M.Ş., H.Y.A., Analysis or Interpretation: B.Ö.D., Ö.P., F.K.Ç., E.D., H.P., M.M., Literature Search: B.Ö.D., E.D., M.Ş., H.Y.A., Writing: B.Ö.D., Ö.P., E.D.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):134-140
DOI: 10.4274/BMJ.galenos.2025.2024.12-1

Research

C-reactive Protein Guided Empirical Antibiotic Therapy Versus Standardized Neutropenic Fever Approach in Patients Undergoing High-dose Chemotherapy Followed by Autologous Stem Cell Transplantation

Yüksek Doz Kemoterapi Sonrası Otolog Kök Hücre Nakli Yapılan Hastalarda C-reaktif Protein Rehberliğinde Ampirik Antibiyotik Tedavisi ile Standart Nötropenik Ateş Yaklaşımının Karşılaştırılması

Ant Uzay[1], Yasemin Gündoğdu[2], Cemal Üstün[3], Yıldız Okuturlar[2], Nigar Rustamova Cennet[4], Hatun Gür[5], Tuğba Yetiş[6], Barış Koşan[2], Süleyman Sami Kartı[1]

[1]Acıbadem University Atakent Hospital, Department of Hematology, İstanbul, Türkiye
[2]Acıbadem University Atakent Hospital, Department of Internal Medicine, İstanbul, Türkiye
[3]Acıbadem Bakırköy Hospital, Clinic of Infectious Diseases, İstanbul, Türkiye
[4]Gazi University Faculty of Medicine, Department of Medical Oncology, Ankara, Türkiye
[5]Kaçkar State Hospital, Clinic of Internal Medicine, Rize, Türkiye
[6]Acıbadem University Faculty of Health Sciences, Department of Nursing, İstanbul, Türkiye

ABSTRACT

Objective: To evaluate the outcomes of C-reactive protein (CRP) guided empirical antibiotic therapy versus standardized neutropenic fever approach in patients undergoing autologous stem cell transplantation.

Methods: Group 1 (n=133) comprised patients who were administered triple combination antibiotic treatment when their plasma CRP levels doubled. Group 2 (n=117) composed of patients who received guideline-based triple combination antibiotic treatment only when fever was detected during neutropenia.

Results: The median duration of neutropenia was 7 days in group 1 (3-18) and group 2 (4-21). The median length of hospital stay was 20 days for group 1 and 18 days for group 2, with similar durations. Fever was encountered in 64.7% of patients within group 1. The median duration of antibiotic therapy until discharge was 9 days in group 1 and 10 days in group 2, with no significant difference observed (p=0.212). One patient in group 1 died, and two patients in group 2 died due to sepsis. In patients who were diagnosed with lymphoma, the median value of the duration of antibiotic therapy until discharge was 10 days in group 1 and 14 days in group 2 (p<0.05).

Conclusion: Our findings demonstrate that empirical antibiotic initiation in this patient group was not beneficial in terms of duration of hospital stay, engraftment periods, duration of antibiotic treatment, and mortality rates. While the strategy was non-inferior to the standardized approach, further research is required for risk stratification and implementation, especially in frail patients with specific diagnoses and comorbidities.

Keywords: Neutropenic fever, empirical antibiotic treatment, C-reactive protein, hematopoietic stem cell transplantation

Address for Correspondence: Yasemin Gündoğdu MD, Acıbadem University Atakent Hospital, Department of Internal Medicine, İstanbul, Türkiye
E-mail: gundogduyase@gmail.com **ORCID ID:** orcid.org/0000-0002-1428-8290

Cite as: Uzay A, Gündoğdu Y, Üstün C, Okuturlar Y, Rustamova Cennet N, Gür H, et al. C-reactive protein guided empirical antibiotic therapy versus standardized neutropenic fever approach in patients undergoing high-dose chemotherapy followed by autologous stem cell transplantation. Med J Bakirkoy. 2025;21(2):134-140

Received: 09.12.2024
Accepted: 14.01.2025
Publication Date: 04.06.2025

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ÖZ

Amaç: Otolog kök hücre nakli yapılan hastalarda C-reaktif protein (CRP) rehberliğinde ampirik antibiyotik tedavisi ile standart nötropenik ateş yaklaşımının sonuçlarını karşılaştırmalı olarak değerlendirmektir.

Gereç ve Yöntem: Grup 1 (n=133), nötropeniye girdikten sonra plazma CRP seviyeleri önceki iki güne kıyasla iki katına çıktığında üçlü kombinasyon antibiyotik tedavisi uygulanan hastalardan oluşuyordu. Grup 2 (n=117) ise nötropenik dönem esnasında ateş tespit edildiğinde kılavuzlara uygun şekilde üçlü kombinasyon antibiyotik tedavisi uygulanan hastalardan oluşuyordu.

Bulgular: Medyan nötropeni süresi her iki grupta 7 gün saptanmıştır (grup 1: 3-18, grup 2: 4-21). Medyan hastanede yatış süresi grup 1 için 20 gün ve grup 2 için 18 gün olup, süreler benzerdir. Grup 1'e hastaların %64,7'sinde ateş gözlemlenmiştir. Medyan antibiyitoik tedavi süresi grup 1'de 9 gün, grup 2'de 10 gün olup, anlamlı bir fark saptanmamıştır (p=0,212). Grup 1'de bir hasta, grup 2'de ise iki hasta sepsis nedeniyle kaybedilmiştir. Lenfoma tanısı alan hastalar ayrıca incelenmiş ve toplam antibiyotik tedavi süresinin medyan değeri grup 1'de 10 gün, grup 2'de ise 14 gün olarak bulunmuştur (p<0,05).

Sonuç: Çalışmamız, bu hasta grubunda standart nötropenik ateş yaklaşımına kıyasla CRP artışına göre ampirik antibiyotik başlanmasının hastanede yatış süresi, engraftman süreleri, antibiyotik tedavi süresi ve mortalite oranları açısından daha faydalı olmadığını göstermektedir. Bu strateji standart yaklaşımdan daha kötü olmamakla birlikte, özellikle belirli tanılara ve komorbiditelere sahip hastalarda uygun risk belirlenmesi ve uygulanabilmesi için daha fazla geniş kapsamlı çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Nötropenik ateş, ampirik antibiyotik tedavisi, C-reaktif protein, hematopoetik kök hücre nakli

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT), the procedure of administering hematopoietic stem cells to quickly restore bone marrow function following high-dose chemotherapy, has been widely used for treating hematological diseases. Although its use has increased patient survival, the risk of infection is an important cause of morbidity and mortality among those undergoing this therapeutic approach. Modifications in HSCT management and better supportive care have resulted in improvements in prevention and successful treatment of infections. The modifications mentioned may be listed as the incorporation of new anti-microbial agents, increased knowledge of immune reconstitution, and development of less toxic conditioning regimens. Despite these advances, infection is the primary cause of death in 8% to 15% of autologous HSCT patients and 17% to 20% of allogeneic HSCT recipients (1).

Following disease relapse, infection is the second most frequent cause of death after autologous HSCT. Patients have the highest risk of infection during the neutropenia period for up to 30 days after bone marrow grafting (2,3). Patients who have undergone autologous HSCT are at the highest risk of infection during the neutropenia period and for up to 30 days after bone marrow grafting. The prolonged neutropenia period and the breach of the mucocutaneous barrier are the main risks for the developing infections (2,4).

Anti-bacterial, anti-viral, and anti-fungal prophylaxis has become a standard measure for protecting HSCT patients against serious infections. The effort to minimize infection-related complications and deaths continues, so the guidelines for prevention and treatment of infections in the HSCT setting are being constantly updated (5). The main focus of the current guidelines is prevention of infections, adequate timing and selection of the anti-infective therapy according to the patients' clinical condition. In common practice, an anti-infective therapy is usually commenced following a febrile episode in neutropenia. Virtually all HSCT patients are under anti-infective prophylaxis at the time of their first febrile episode. Usually, the prodromal period of the infection is short and may remain unnoticed due to symptoms overlapping with the conditioning regimen. The most common initial symptom of the infection in patients is high fever, sometimes accompanied by systemic inflammatory response syndrome features. The guidelines postulate urgent commencement of broad spectrum antibiotics after obtaining adequate culture samples and supportive care as an initial approach for HSCT patients with neutropenic fever (2). The vast majority of the patients benefit from this and fully recover after neutrophil engraftment, but some patients still develop septic shock and die before neutrophil recovery despite seemingly appropriate treatment.

C-reactive protein (CRP) is a valuable and commonly used marker for inflammation, particularly infection severity. To predict the risk of fatal infections in neutropenic HSCT patients, some researchers have studied the impact of the CRP levels on infection-related mortality of the allogeneic and autologous HSCT patients (6). In a recent review, Massaro and colleagues researched the value of different biomarkers as predictors for infection and mortality in febrile neutropenic HSCT patients (7). In some of the major studies included in the review, elevation of CRP levels was associated with increased risk of death from infection and was well correlated with bloodstream infections (7,8). CRP levels commonly rise shortly after the level of IL-6 is elevated. This usually occurs before the body temperature starts to increase; thus, a CRP surge can be the first sign

of an ongoing infectious process. Given the importance and the usefulness of CRP as an early predictor of serious infections, we hypothesized that early empirical anti-bacterial therapy based on the increasing CRP levels, before the febrile response, may reduce the incidence and duration of neutropenic fever in autologous HSCT patients.

METHODS

Patient Selection

In this single-center observational retrospective study, 250 patients who underwent autologous HSCT due to lymphoma or multiple myeloma were enrolled. Age, gender, remission status, number of previous chemotherapies, Hematopoietic Cell Transplantation-Comorbidity index score, and baseline CRP levels were recorded upon admission. Those who had clinical evidence of any infection, decreased renal function, cardiac event within the past three months, and unexplained high CRP levels were excluded from the study. Since the requirements for autologous HSCT necessitate at least partially controlled primary malignancy, patients with active lymphoma and myeloma were not included in the study. Primary prophylaxis with valacyclovir 500 mg/d starting on day-7, levofloxacin 500 mg/d on day-5 and fluconazole 100 mg/d starting after the transplant day was given to all patients until neutrophil engraftment (>500/mm^3). In some patients who had neutropenic fever under primary prophylaxis, levofloxacin was changed to amikacin, and a few patients required broad spectrum anti-fungal therapy with caspofungin or liposomal amphotericin B instead of fluconazole.

A total of 133 patients who underwent autologous HSCT between 2016 and 2018 were enrolled to receive triple combination antibiotic treatment with piperacillin/tazobactam, amikacin, and teicoplanin when their plasma CRP levels doubled compared to the CRP levels on the previous two days after neutropenia had commenced. This group who started antibiotic treatment according to CRP trend was named group 1. In the neutropenic patients whose CRP levels did not increase significantly and who had febrile episodes, the same triple combination antibiotic therapy was commenced at the time of fever. Samples for aerobic and anaerobic blood culture, urine culture, and sputum culture were obtained in advance from all patients according to their symptoms who received triple antibiotic therapy. The patients who remained afebrile during the neutropenia period and had maintained normal CRP levels continued with the primary prophylaxis until neutrophil engraftment.

Apyrexial patients with a rapid increase in CRP levels preceding neutropenia were followed without changing the primary prophylaxis, as long as their neutrophils remained above 500/mm^3. Those patients were administered triple antibiotic treatment after they entered neutropenia even in the absence of fever. Before the neutropenic period, development of a febrile condition without an evident infection locus and without concurrent CRP increase was not an indication for empirical antibiotic therapy.

After a neutropenic patient was administered triple antibiotic therapy based on CRP levels, further antibiotic modification was performed according to the culture and antibiotic susceptibility results, or if there was breakthrough fever with no clinical response to the ongoing treatment. Antibiotics were discontinued if the patient had a neutrophil count greater than 1000/mm^3, and remained clinically stable and afebrile for at least 48 hours.

A total of 117 patients who underwent autologous HSCT between 2012 and 2015 were administered empirical triple combination antibiotic therapy at the time of first episode of neutropenic fever, regardless of the CRP levels, in accordance with the latest Infectious Diseases Society of America guideline (9). Treatment was modified based on the results of the culture and antibiotic susceptibility testing and if there was no initial clinical response to the primary anti-infective treatment. This group was named group 2, and both groups received the same conditioning regimens and primary prophylaxis.

Stem Cell Harvesting

Patients diagnosed with myeloma underwent stem cell mobilization with filgrastim 10 mcg/kg for 5 days, with the exception of patients who had insufficient peripheral CD34+ cells on day 4 of mobilization. The mentioned patients were mobilized 3 weeks later, with plerixafor and filgrastim.

Stem cell harvesting was performed after second line salvage chemotherapy followed by filgrastim in patients who were diagnosed with lymphoma.

Conditioning Regimens

Melphalan 200 mg/m^2 on day-2 was administered as a conditioning regimen before autologous HSCT in patients diagnosed with multiple myeloma. Dose reduction to 140 mg/m^2 was performed in patients who had creatinine clearance below 50 mL/min.

Patients diagnosed with Hodgkin's disease and non-Hodgkin lymphoma received the BEAM protocol (BCNU 300 mg/m^2, on day-7; etoposide 200 mg/m^2, and ARA-C 200 mg/m^2/bid, between day-6 and -3; MLN 140 mg/m^2, on day-2) as

a conditioning regimen. Stem cell infusion was performed on day 0 following premedication for infusion reactions with acetaminophen, diphenhydramine, and prednisolone.

This study was approved by Acıbadem University Ethics Committee (approval no: 2024-9/361, date: 30.05.2024) and written informed consent was obtained from each patient.

The clinical and laboratory data obtained from these patients were recorded and compared statistically. The primary end points of this study were to investigate whether there was a positive effect of initiating empirical antibiotic therapy based on the surge of CRP levels, on the death rate due to infection, the number of febrile neutropenic days, and hospitalization duration in patients undergoing autologous transplant. The secondary endpoint was to investigate whether shorter antibiotic treatment periods and fewer breakthrough febrile episodes, with fewer changes in the anti-infective regimen, could be achieved in group 1 compared to the patients who were given empirical antibiotics based on the classical indications for treatment of neutropenic fever.

Statistical Analysis

The statistical analysis was performed with SPSS version 26.0 (IBM Corp., released 2019, IBM SPSS Statistics for Macintosh, Version 26.0) and a value of $p<0.05$ was considered statistically significant. The normality of the variables was assessed using the Shapiro-Wilk test.

RESULTS

A total of 250 patients were included; 133 patients were in group 1, who were given empirical antibiotic treatment following a threefold increase in their CRP levels (Table 1). Group 2, which included patients who received a guideline-based standardized approach, consisted of 117 patients. The median age of the patients in group 1 was 55 (range: 18-76), while it was 58 (range: 21-73) in group 2, and there was no significant difference between the two groups ($p=0.632$). The median length of hospital stay was 20 days in group 1, while it was 18 days in group 2. Median duration of neutropenia was 7 days in group 1 (3-18) and group 2 (4-21). In group 1, fever was encountered in 90 out of 133 patients (64.7%). The mean number of days with fever was 3.14 in group 1 and 1.01 in group 2, and a significant difference was detected ($p<0.05$). Median day of neutrophil engraftment was 11 in group 1 and 9 in group 2, and a clinically significant difference was not observed. As consecutive CRP testing was not performed on patients in group 2, a baseline CRP level was only available for group 1 and it was calculated as 0.47 (normal value <0.5 mg/dL). The median day of the detection of a threefold increase in CRP was 5±1.71 days in group 1. The median CRP level at discharge was 2.02±1.86 in group 1. Median day of platelet engraftment was 13 in group 1 and 11 in group 2, and a significant difference was not detected.

The median value of the total duration of antibiotic treatment until discharge was 9 days in group 1 and 10 days in group 2, and a significant difference was not detected ($p=0.212$). The type of antibiotic treatment was escalated in a total of 70 (52.6%) patients within group 1, compared to 27 (23%) patients within group 2.

Anti-fungal treatment was administered to 22 (19%) patients in group 1 while 4 patients received anti-fungals in group 2 (0.3%) ($p=0.001$). Anti-viral treatment was not required in any patient. One patient in group 1 died, while two patients died due to sepsis in group 2, despite ICU admission.

Multiple myeloma was the most frequent diagnosis with a total of 162 patients, with the two groups combined. The patients who were diagnosed with multiple myeloma were further investigated, and the median length of hospital stay was 18 days in group 1 (n=84) while it was 16 days in group 2 (n=78) ($p<0.05$). Median duration of neutropenia was 6 days in group 1 (4-13) and group 2 (4-18). The mean number of days with fever was 2.62 in group 1 and 0.54 in group 2, which was statistically significant ($p<0.05$). The median day

Table 1. Patient characteristics and end points analysis

	Group 1 (n=133)	Group 2 (n=117)	p-value
Age, median (min-max)	55 (18-76)	58 (21-73)	0.632
Length of hospital stay, median days (min-max)	20 (13-47)	18 (12-66)	**0.0001**
Duration of neutropenia, median days (min-max)	7 (3-18)	2 (4-21)	0.059
Number of days with fever, mean	3.14	1.01	**0.0001**
Neutrophil engraftment, median days	11	9	**0.0001**
Platelet engraftment, median days	13	11	**0.0001**
Duration of antibiotic treatment, median days	9	10	0.212
Anti-fungal treatment administered n (%)	22 (19)	2 (0.3)	**0.0001**

min: Minimum, max: Maximum

of neutrophil engraftment was 11 in group 1 and 8 in group 2 ($p<0.05$).

A total of 88 patients were diagnosed with lymphoma. Out of these, 44 patients were in group 1, while 39 patients were in group 2. The subset of patients who were diagnosed with lymphoma was analyzed, and the median length of hospital stay was calculated as 22 days for both groups. The median duration of neutropenia was 8 days in group 1 (3-18) and 10 days in group 2 (6-21). The mean number of days with fever was 4.05 in group 1 and 1.95 in group 2 ($p<0.05$). Median day of neutrophil engraftment was 10 in group 1 and 12 in group 2 ($p<0.05$). The median value of the total duration of antibiotic treatment until discharge was 10 days in group 1 and 14 days in group 2 ($p<0.05$).

Blood culture was obtained from 116 patients within group 1, and a positive blood culture was detected in 16 (13.8%) (Table 2). Culture studies were performed on all of the 117 patients within group 2, and 39 (33.2%) patients had a positive blood culture. If remission was not achieved within 48 hours, a second blood culture was performed. A second culture was required for 50 patients among group 1, and positive culture results were obtained from 5 patients. In group 2, 116 patients required second blood cultures and positive results were detected in 12 patients. If satisfactory clinical or biochemical response was not achieved after the second culture, a third blood culture was performed. A third culture was performed in 13 patients in group 1. One patient's blood culture was positive. A third blood culture was not required for 120 patients in group 1. In group 2, a third blood culture was performed on 114 patients, and 5 patients had positive results. The median days for the total duration of indwelling catheters was 20.1 in group 1 and 16.1 in group 2.

Among the 16 patients who had positive first blood cultures, 19 microorganisms were detected with the culture studies, in group 1. Within this patient population, *Staphylococcus epidermidis* was detected in 11 (57%) patients and *Staphylococcus hominis* was detected in 4 (21%) patients. Among the reaiming 4 cultures, each of the microsoganisms *Streptococcus viridans, Staphylococcus aureus,* extended-spectrum beta-lactamase producing *Escherichia coli* and *Globicatella sanguinis* was detected once (0.5%).

Within group 2, microorganisms were identified from all 39 first blood cultures. Within this patient population, *Staphylococcus epidermidis* was detected in 14 (35%) patients, *Escherichia coli* was detected in 9 (23%), *Staphylococcus aureus* was identified in 5 (12%) patients, and *Staphylococcus hominis* was identified in 4 (20%) patients. The bacterial isolates identified were *Clostridium difficile* in 3 (7%) patients and *Staphylococcus haemolyticus* in 2 (5%) patients. *Klebsiella pneumoniae* and *Candida species* was detected once (0.2%).

DISCUSSION

Prompt management of febrile neutropenia is especially critical for patients with hematological malignancies due to their higher risk of mortality from severe infections (10). In harmony with guideline-directed medical therapy, the onset of fever has been the cornerstone of broad-spectrum antibiotic treatment initiation. Despite early initiation of antibiotic treatment after detection of fever, mortality rates range from 10% to 30% in this patient population, and patients with comorbidities have the highest risk (11,12). As the capacity to generate an inflammatory response is hindered, some patients may not demonstrate signs and symptoms of infection, especially in the early days, resulting in a delay in treatment. We aimed to investigate the outcomes of an alternative approach that used preemptive antibiotic treatment in the setting of CRP doubling before the development of fever, and to compare the outcomes of the cohort that was treated with a standardized approach.

One of the prominent differences between two groups was that fever was not detected in 47 patients within group 1 (35.3 %). Among the 47 patients who were afebrile throughout their hospital stay, 34 were diagnosed with multiple myeloma while 13 were diagnosed with lymphoma. As antibiotic treatment was empirically started, sepsis, septic shock, or other manifestations of invasive infection may have been prevented. It is well-established data that neutropenic fever is encountered in more than 80% of

Table 2. Blood culture outcomes

	Group 1 (n= 133)	Group 2 (n= 117)
Blood culture obtained (%)	116 (87.2)	117 (100)
No of patients with positive first blood culture (%)	16 (13.8)	39 (33.2)
Second blood culture obtained (%)	50 (37.6)	116 (99.1)
No of patients with positive second blood culture (%)	5 (10)	12 (10.3)
Third blood culture obtained (%)	13 (9.8)	114 (97.4)
No of patients with positive third blood culture (%)	1 (7.7)	5 (4.4)

patients with hematologic malignancy (9). In our study, as only 65.7% of the patients developed fever within group 1, severe infection risk may have been reduced in a substantial number of patients. This risk reduction was more prominent in patients who were diagnosed with multiple myeloma since most of the afebrile patients had this diagnosis. This finding may be associated with the fact that the duration of neutropenia is generally lower in myeloma patients compared to patients diagnosed with lymphoma (13).

In a study where the outcomes of empirical and preemptive anti-fungal treatment during neutropenic fever were compared in patients with hematologic malignancies, the mortality rates were 97.1% and 94.6% respectively (p=0.305) (14). Even though there was not a significant difference between mortality rates, invasive fungal infection was detected 9.2% in the preemptive group, while it was 2.2% in the empirical treatment group. Similar to our study, Yuan et al. (14), postulated that empirical treatment in this vulnerable patient population may be effective in the prevention of invasive infections.

The median durations of antibiotic treatment were similar for both groups, were 9 days and 10 days for group 1 and group 2, respectively. Therefore, in terms of treatment duration, we concluded that the empirical approach was not favorable compared to the standardized approach. However, when we further analyzed these data for lymphoma patients, the median durations of antibiotic treatment were 10 days for group 1, while it was 14 days for group 2 ($p<0.05$). As most of the patients who were diagnosed with lymphoma were more frail due to a history of recurrent chemotherapy, and as most of these patients were not in complete remission; this patient population is more vulnerable to infections due to issues like longer neutropenia periods. Consequently, for a subset of patients with lymphoma from our study, this empirical strategy may be beneficial to alleviate the severe burden of infection.

Additionally, while 70 patients required antibiotic treatment escalation within group 1, only 27 patients required escalation within group 2. In our study, the early initiation of antibiotic treatment was associated with treatment escalation. Anti-fungal treatment was administered to 19% and 0.3% of the patients in groups 1 and 2, respectively. Overall, our study demonstrated that broader spectrum antibiotic treatment, along with higher rates of anti-fungal treatment, were used when the empirical approach was implemented.

The median length of hospital stay and the duration of neutropenia were similar in both groups. The median days of neutrophil engraftment and platelet engraftment were also similar between both groups. Mortality rates were 0.75 and 1.7 for groups 1 and 2, respectively, and a clinically significant difference was not detected. A positive blood culture result was obtained in 13.8% of the patients in group 1, while 33.2% of the patients in group 2 had positive culture results.

Study Limitations

This study has several limitations. Besides the small sample size and the lack of random sampling, a retrospective analysis was performed, which may have resulted in bias.

CONCLUSION

Our data demonstrate that empirical antibiotic initiation within this patient population was not favorable in terms of duration of hospital stay, engraftment periods, duration of antibiotic treatment, and mortality. This strategy may be considered for patients with certain diagnoses and comorbidities, taking into account the frailty of patients. This study showed that the empirical treatment strategy was non-inferior to the standardized approach. More research is needed to perform proper risk stratification and implementation in the future.

ETHICS

Ethics Committee Approval: This study was approved by Acıbadem University Ethics Committee (approval no: 2024-9/361, date: 30.05.2024).

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

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: A.U., C.Ü., N.R.C., H.G., T.Y., B.K., S.S.K., Concept: A.U., C.Ü., Y.O., B.K., S.S.K., Design: A.U., C.Ü., B.K., S.S.K., Data Collection or Processing: Y.G., Y.O., N.R.C., H.G., Analysis or Interpretation: A.U., Y.G., C.Ü., Y.O., T.Y., S.S.K., Literature Search: Y.G., N.R.C., T.Y., Writing: A.U., Y.G.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):141-148
DOI: 10.4274/BMJ.galenos.2025.2024.8-14

Research

Neutralizing Antibodies and COVID-19: Predicting Disease Duration and Severity After Vaccination and Infection

Nötralizan Antikorlar ve COVID-19: Aşı ve Enfeksiyon Sonrası Hastalığın Süresi ve Şiddetinin Öngörüsü

Rüveyda Alacahan Dürer[1], Kadriye Kart Yaşar[2,3], Esra Canbolat Ünlü[3], Muhammet Salih Tarhan[3]

[1]University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Department of Medical Mircobiology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Department of Infectious Disease, İstanbul, Türkiye
[3]University of Health Sciences Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Türkiye

ABSTRACT

Objective: This study aimed to explore the correlation between neutralizing antibodies post-Coronavirus disease-2019 (COVID-19) infection and vaccination with demographic characteristics, disease progression, severity, and diagnostic parameters.

Methods: A total of 80 COVID-19 patients with positive real-time polymerase chain reaction (RT-PCR) test and other diagnostic parameters were included in the study. Patients were grouped based on demographic characteristics, comorbid disease status, disease and pneumonia severity, vaccination status, intensive care requirements, and laboratory parameters used in diagnosis and follow-up. Serum samples collected on day 18 after the RT-PCR positive result were analyzed using VIDAS anti-SARS-CoV-2 immunoglobulin G (IgG) and immunoglobulin M (IgM) kits on the VIDAS analyzer (bioMérieux, France). Statistical analyses were conducted using the IBM SPSS 25.0 software package, and a significance level of less than 0.05 was considered.

Results: The results showed that patients with two or more vaccine doses had higher IgG titers compared to those with one or no dose. Patients over 65 had higher IgG titers than those younger than 65. Intensive care unit patients had lower IgG titers than ward-treated patients. Critically ill patients exhibited elevated IgM and IgG titers compared to moderate and severe cases. Additionally, patients with hypertension had higher IgG titers. A strong positive correlation was found between diagnostic biomarkers and neutralizing antibody titers.

Conclusion: Antibody titers increased with disease severity, though their neutralizing capacity remains uncertain. Our results are consistent with the literature, and our study is among the few studies that have examined the relationship between the kinetics of neutralizing antibodies and prognostic biomarkers.

Keywords: Coronavirus disease-2019, neutralizing antibody, disease severity, diagnostic biomarkers, comorbidity

ÖZ

Amaç: Bu çalışmada Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu ve aşılamasını takiben oluşan nötralizan antikorların; çalışmaya dahil edilen hastaların demografik özellikleri, hastalığın seyri, şiddeti ve diğer tanısal parametrelerle ilişkisinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) testi ve diğer tanısal parametreleri pozitif 80 COVID-19 hastası dahil edilmiştir. Hastalar; demografik özellikleri, komorbid hastalık durumu, hastalık ve pnömoni şiddeti, aşılama durumları, yoğun bakım gereksinimleri, tanı ve izlemde kullanılan laboratuvar parametreleri sonuçlarına göre gruplandırılmıştır. RT-PCR pozitifliğini takiben 18. günde alınan serum örnekleri, VIDAS® Anti-SARS-CoV-2 immünoglobülin G (IgG) ve immünoglobülin M (IgM) kitleri kullanılarak VIDAS analizöründe (bioMérieux, Fransa) çalışılmıştır. İstatistiksel analizler IBM SPSS 25.0 paket programı ile yapılmış, anlamlılık düzeyi <0,05 olarak dikkate alınmıştır.

Bulgular: Hastalardan iki ve daha çok dozda aşılanmış olanların oluşturdukları IgG titreleri hiç aşı olmamış veya bir doz aşılanmış olanlara göre daha yüksek bulunmuştur. 65 yaş üzerindeki hastaların IgG titreleri Altmış beş yaş ve altı hastalara göre daha yüksektir. Yoğun bakım ünitesi'nde tedavi görenlerin IgG titreleri serviste takip edilenlere göre daha düşüktür. Kritik hastaların oluşturdukları IgM ve IgG antikor titrelerinin orta ve

Address for Correspondence: Rüveyda Alacahan Dürer, PhD, University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Department of Medical Mircobiology, İstanbul, Türkiye
E-mail: ruveyda.alacahan@sbu.edu.tr **ORCID ID:** orcid.org/0000-0001-2345-6789

Cite as: Alacahan Dürer R, Kart Yaşar K, Canbolat Ünlü E, Tarhan M. Neutralizing antibodies and COVID-19: predicting disease duration and severity after vaccination and infection. Med J Bakirkoy. 2025;21(2):141-148

Received: 10.09.2024
Accepted: 10.01.2025
Publication Date: 04.06.2025

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ÖZ

şiddetli hasta grubuna kıyasla daha yüksek olduğu tespit edilmiştir. Hipertansiyonu olan hastaların IgG titreleri daha yüksektir. Hastaların tanısal biyobelirteçleri ile nötralizan antikor titreleri arasındaki ilişkide CRP, ferritin, D-dimer, PLT, NLR, MLR ve PLR düzeyleriyle IgG titreleri arasında pozitif yönde yüksek düzey korelasyon gözlenmiştir. (tüm değerler için p<0,05'tir).

Sonuç: COVID-19'da hastalık şiddeti arttıkça oluşturulan antikor titreleri de artmaktadır. Fakat bu antikorların nötralize edici fonksiyonları ne derece yansıttıkları konusu hala tartışmalıdır. Verilerimizin tümü literatürle paralellik göstermekle birlikte hastalıkla oluşan nötralizan antikorların miktarının özellikle prognostik biyobelirteçlerle ilişkisini de irdeleyen literatürdeki sayılı çalışmalardandır.

Anahtar Kelimeler: Koronavirüs hastalığı-2019, nötralize edici antikor, hastalık şiddeti, tanısal biyobelirteçler, komorbidite

INTRODUCTION

The gold standard for rapid detection and diagnosis of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral nucleic acid is real-time polymerase chain reaction (RT-PCR). The use of RT-PCR is limited due to its time-consuming and laborious nature, as well as the requirement for specialized equipment and experienced personnel. Especially in regions with limited laboratory facilities. (1). Serological tests are complementary methods that can be used when viral RNA cannot be detected. Also, these tests are preferred for rapid screening of large populations. Both molecular and serological tests are essential to guide antiviral therapy, epidemiological measures, vaccination, and ultimately disease control by implementing appropriate strategies (2,3). For the diagnosis of viral infections, it is common to use the human antibody response. In comparison with RT-PCR assays, antibody detection is generally faster, cheaper, easier to use, more accessible, and requires less laboratory expertise. In spite of these practical advantages of serological tests, the antibody responses to SARS-CoV-2 are still poorly understood and the clinical utility of these tests requires further research (4). Plasma levels of interleukin 2 (IL2), IL6, IL7, IL10, Granulocyte colony-stimulating factor, and IP10 are observed to be higher in patients with severe disease compared to those with a less severe prognosis infected with SARS-CoV-2. In these patients, MCP1, MIP1A, tumor necrosis factor alpha, lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP), and D-dimer values are high, and the lymphocyte count is low (5,6). Few studies have reported on the kinetics of neutralizing antibody (Nab) responses in severe cases, and whether this antibody response has a correlation with disease prognosis. We investigated the possible relationship between responses in severe and mild cases and various prognostic parameters to fill this gap in the literature.

METHODS

Study Design

The present study was observational and cross-sectional.

Ethical Considerations

The study was approved The study was approved Health Sciences University Hamidiye Scientific Research Ethics Board (decision no: 24/25, date: 09.07.2021). The study was conducted in accordance with the principles of the Declaration of Helsinki The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent

Written informed consent was obtained from patients to participate in this study. In accordance with the regulatory procedures of the study clinic, patients gave written informed consent for the processing and publication of their medical records (anonymized) for scientific purposes.

Participants

The study analyzed 80 COVID-19 patients with positive RT-PCR results and other diagnostic tests. Patients were categorized according to demographic characteristics, comorbid disease status, severity of disease, including pneumonia, vaccination status, intensive care unit requirements, and laboratory parameters used for diagnosis and follow-up. The severity of COVID-19 was defined according to the World Health Organization (WHO) criteria as follows:

Moderate: Clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including oxygen saturation (SpO_2) ≥90% on room air.

Severe: Clinical signs of pneumonia plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, or SpO_2 <90% on room air.

Critical: Acute respiratory distress syndrome (ARDS), sepsis, or septic shock All patients who signed the informed consent

form were included in the study. Serum samples collected on the 18th day after RT-PCR positivity were analyzed using VIDAS anti-SARS-CoV-2 immunoglobulin G (IgG) and immunoglobulin M (IgM) kits (Biomérieux, France) on the VIDAS analyzer.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS 25.0 software and the significance level was set at <0.05.

RESULTS

The patient group included 52.5% females. Eighty-one point two percent of the patients were over 65 years of age. The average age of patients treated in the intensive care unit (ICU) is 82.4, and the average age of patients treated in the ward is 71.9. Forty percent of the patients had received at least three doses of COVID-19 vaccine, Twenty-eight point seventy-five percent were unvaccinated. Twelve point five percent of the patients were monitored and treated in the ICU; the rest in the ward. Sixty-six (82.5%) of the included patients were classified as severe or critical cases. Seventy-six point three percent of the patients had at least one comorbid condition (Table 1). Hypertension (HT) was the most common comorbidity, affecting 57.5% of the sample. The means for CRP, ferritin, procalcitonin, D-dimer, fibrinogen, neutrophil lymphocyte ratio (NLR), monocyte lymphocyte ratio (MLR), and platelet lymphocyte ratio (PLR) were significantly higher than the reference values.

Based on the Mann-Whitney U test comparing the total number of vaccinations to IgM and IgG antibody titers, patients who received 2 or more vaccinations had significantly higher IgG antibody titers than unvaccinated patients (z=-5.177; p<0.05) (Table 2).

The IgG antibody titer of patients treated in the ICU was found to be significantly lower than that of patients followed and treated in the ward (z=-2.62, p<0.05) (Table 3).

There was a significant difference between median IgM titers and patient severity, with severe patients having statistically higher IgM titers than moderate patients (χ^2=9.337; p<0.05). Similarly, the median IgG titer was higher in critically ill patients than in patients in the moderate and severe groups (χ^2=21.831; p<0.05) (Table 4).

Analysis showed no significant difference in IgM and IgG antibody titers according to comorbidity. However, a statistically significant difference was found in the analysis

Table 1. Demographic characteristics of the patients

	Patients (n=80)
Sex	
Woman n (%)*	38 (47.5)
Men n (%)	42 (52.5)
Age	
≤65 n (%)	15 (18.8)
>65 n (%)	65 (81.2)
Admission ICU**	
Yes n (%)	10 (12.5)
No n (%)	70 (87.5)
Disease severity	
Moderate n (%)	14 (17.5)
Severe n (%)	59 (73.7)
Critical n (%)	7 (8.8)
Comorbidity	
Yes n (%)	61 (76.3)
No n (%)	19 (23.7)
Vaccination status	
0-1 n (%)	23 (28.75)
2 n (%)	25 (31.25)
≥ 3 n (%)	32 (40)
***Row percentage**	
**ICU: Intensive care unit	

Table 2. Mann-Whitney U test for IgM and IgG titers by vaccination status

Antibody	Total doses	N	Q_1-Q_3 (median)	U	z	p-value
IgM	0	23	0.27-1.76 (0.43)	595	-0.643	0.52
	≥2	57	0.30-2.20 (0.80)			
IgG	0	23	1.09-23.71 (8.08)	168.5	-5.177	**0.001**
	≥2	57	49.33-57.93 (56.07)			

Table 3. Mann-Whitney U test for IgM and IgG titer based on ICU status

Antibody	ICU	N	Q_1-Q_3 (median)	U	z	p-value
IgM	No	70	0.30-2.60 (0.74)	263.5	-1.259	0.208
	Yes	10	0.22-0.87 (0.43)			
IgG	No	70	23.60-57.69 (54.56)	170	-2.61	**0.009**
	Yes	10	0.84-23.49 (3.74)			

performed between the highest rate of comorbidity (HT) and neutralizing antibodies (Nab). Patients with HT produced lower levels of IgM and IgG antibodies (z=-2.044; p<0.05, z=-7.611; p<0.05) (Table 5).

Correlation analysis was performed to examine the relationship between IgM and IgG antibody titers, and levels of biomarkers known to be prognostic for COVID-19. A moderate positive correlation was found between IgG titer and CRP level (r=0.276; p<0.05). Positive and moderate correlations were also observed between IgG titer and ferritin, D-dimer and PLT (r=0.235, p<0.05; r=0.318, p<0.05; r=0.310, p<0.05). Similarly, positive and moderate correlations were observed between NLR, MLR, and PLR values and IgG titers (r=0.201; p<0.05; r=0.247; p<0.05; r=0.547; p<0.05, respectively) (Table 6).

DISCUSSION

The primary target of SARS-CoV-2 Nab is the S antigen, comprising S1 and S2 subunits. Thus, neutralizing the RBD in the S1 region of the virus is crucial in preventing infection. However, it is unclear which immune components are most important during viral infection and what antibody levels are required for a healthy immune response (7).

Most individuals infected with COVID-19 produce Nab through humoral immunity mechanisms. However, the

Table 4. Kruskal-Wallis test for IgM and IgG titers by disease severity

Antibody	Disease severity	N	Q_1-Q_3 (median)	χ^2	s.s	p-value
IgM	Moderate	14	0.14-0.43 (0.24)	9.337	2	0.009
	Severe	59	0.34-2.46 (0.83)			
	Critical	7	0.30-8.62 (0.49)			
IgG	Moderate	14	0.25-4.20 (1.62)	21.831	2	**<0.001**
	Severe	59	32.41-57.46 (54.64)			
	Critical	7	58.91-59.80 (59.37)			

Table 5. Mann-Whitney U test for IgM and IgG titers in relation to the presence of HT

Antibody	HT*	N	Q_1-Q_3 (median)	U	z	p-value
IgM	No	34	0.36-4.30 (1.06)	572	-2.044	0.041
	Yes	46	0.24-1.79 (0.51)			
IgG	No	34	33.04-57.99 (55.15)	0.001	-7.611	**0.001**
	Yes	46	4.81-44.79 (14.5)			

*HT: Hypertension

Table 6. Correlation analysis of IgM and IgG titers with diagnostic biomarkers

		IgM	IgG
CRP	r	0.17	0.276*
	p	0.132	**0.013**
Ferritin	r	0.043	0.235*
	p	0.704	**0.036**
PLT	r	0.015	0.31
	p	0.896	**0.005**
D-dimer	r	-0.011	0.318
	p	0.92	**0.008**
NLR	r	0.114	0.201
	p	0.316	**0.015**
MLR	r	-0.095	0.247
	p	0.402	**0.028**
PLR	r	0.122	0.145
	p	0.281	**0.015**

*p<0.05

duration and capacity of the humoral immune response is not fully known. Studies have shown that neutralizing and protective anti-SARS-CoV-2 antibodies are produced after infection, and that these antibodies reduce the risk of reinfection within 1-3 months of infection. Studies measuring Nab have shown that antibodies are detectable approximately 6 days after symptom onset, increase over the next 3-4 weeks, and that seroconversion occurs 2 weeks after infection in most patients (8).

Neutralization tests (NTs), on the other hand, provide an indication of whether antibodies produced after exposure to SARS-CoV-2 can neutralize the virus, and the level of protection provided by these antibodies in the event of subsequent exposure. NTs for detecting and measuring NAbs produced against the virus are the golden standard. The NTs assay has been conducted using SARS-CoV-2 viruses produced in cell culture. The need for specialized personnel and high-security laboratory conditions to perform these tests limits their practical use (9).

Compared to RT-PCR and NTs tests in diagnosis, antibody detection is faster, cheaper, easier to use, and therefore more accessible. Quantitative serological tests quantify the titer of the immune response by measuring antibody responses after SARS-CoV-2 infection and vaccination (10). These results are valuable tools for investigating the relationship between antibody responses and disease severity, asymptomatic infection, as well as humoral responses (11,12).

Our study investigated the kinetics of NAbs in hospitalized RT-PCR-positive patients and the association of antibody positivity with demographics, comorbidity status, disease course, severity, and other laboratory parameters.

In our study, 52.5% of the patients were female and 47.5% were male. All patients included in the study were hospitalized. Out of the 80 patients, only five (6.25%) did not produce a response (IgM and/or IgG). All these patients were female, over 65 years of age, and had at least one comorbidity (HT), were followed in the ICU, had a World Health Organization (WHO) severity of illness classification of severe, and had severe pneumonia. The remaining patients (93.75%) had detectable levels of IgM and IgG.

Research has demonstrated that age is the most important risk factor for serious illness and death from COVID-19. Upon reviewing the literature on this topic, researchers observed varying outcomes. Young et al. (13) conducted a study on 181 COVID-19 patients and found no association between patient age and levels of IgG, IgM, and IgA antibodies. A study by Luo et al. (14) of 678 COVID-19 patients found that IgM and IgG antibody titers increased significantly with age and reported that older patients had stronger immune responses to SARS-CoV-2 than younger patients. In a study in our country, it was reported that one of the factors influencing the antibody response was age, and the titers developed against the disease were found to increase with age (15). In our study, 81.2% (65/80) of the 80 COVID-19 patients were older than 65 years, similar to the study by Ozgocer et al. (15). However, according to our results, although the median IgM titer in patients over 65 years (1.76) was higher than that in patients 65 years and younger (0.57), this difference was not statistically significant ($z=-1.923$; $p>0.05$). The median IgG antibody titer (54.64) in patients over 65 years of age was statistically significant higher than the median (18.39) in patients 65 years and younger ($z=-1.824$; $p<0.05$). According to these results, our study showed that there was a correlation between IgG antibody titer and age, indicating that IgG levels increased with age.

The immune response to infectious diseases occurs in two ways. The acquisition of immunity can occur in two ways: the first is after exposure to the microorganism causing the infection, and the second is possible with vaccination. There have been many studies examining the Nab that develop in response to COVID-19 infection and those that develop after vaccination (16-18). While both situations develop protective antibodies against the disease, vaccination significantly reduces mortality from COVID-19 infection, especially in those with comorbidities. This reduction in mortality also leads to a decrease in transmission and severity of the disease.

Among the patients included in our study, 28.75% were never vaccinated, 31.25% were vaccinated with two doses, and 40% were vaccinated with three or more doses. When we evaluated IgM and IgG antibody titers according to total vaccination status, the median value of IgM titers did not show a significant difference total vaccine dose ($z=-0.643$; $p>0.05$). When we performed the same evaluation for IgG antibodies as in similar studies in the literature, the median IgG titer of patients who had received at least two doses of vaccine (56.07) was significantly higher than that of patients who had never been vaccinated (8.08) ($z=-5.177$; $p<0.05$).

Nab levels were found to be higher in ICU patients compared to other patients in most studies investigating the relationship between Nab levels produced by COVID-19 patients and their ICU hospitalization status (19-22). In contrast, IgG antibodies were reported to be significantly lower in ICU patients than in other patients in another study of 38 patients, of whom 11 were ICU patients (23).

Within the 80 patients included in the study, 12.5% were ICU patients who were followed in the ward. The median IgM antibody titer of ICU patients (0.43) did not differ significantly from that of other patients (0.74). However, the median IgG titer of ICU patients (3.74) was significantly lower than that of patients followed in the ward (54.56) (z=-2.16; p<0.05). Similar to the study by Sun et al. (23), our study found that critically ill COVID-19 patients being cared for in the ICU were unable to generate a sufficient level of IgG-type response. However, it is important to note that both the 80 patients in our study and the 10 patients were monitored in the ICU were of a higher mean age, compared to similar studies in the literature. Therefore, low IgM and IgG titers may have been detected in our patients, independent of COVID-19, in relation to inadequate immune response due to advanced age.

Several studies have demonstrated a correlation between the severity of COVID-19 and the antibody response. In a study of 30 COVID-19 patients, it was found that those with symptomatic and severe cases of the disease had a higher Nab response than those with asymptomatic and mild cases. Additionally, the study noted that Nab in mild cases disappeared more quickly than in severe cases (24).

A study reported significantly higher antibody titers in 285 patients in China in patients with severe COVID-19 than in those with mild and moderate disease (4). Tan et al. (25) also found a significant increase in titers with increasing severity of disease and pneumonia.

When classifying the patients in our study according to disease severity based on the WHO criteria, 14 out of 80 (17.5%) were moderate, 59 out of 80 (73.7%) were severe, and seven out of 80 (8.8%) were critical. The Kruskal-Wallis test was used to evaluate the relationship between disease severity and antibody titer. A significant relationship was found between IgM and IgG antibodies and disease severity (χ^2=9.337; p<0.05) and (χ^2=21.831; p<0.05). The levels of Nabs in the critical patient group were significantly higher than those in the severe and moderate patient groups. The Mann-Whitney U test was used to determine the significance of this difference between the paired groups (moderate-severe/critical-moderate/severe-critical). Based on this grouping, it was found that the IgM and IgG antibody titers of severe patients were significantly higher than those of moderate patients (z=-3.524; p<0.15, z=-5.633; p<0.05). While IgM levels were not significantly different between critical and moderate patients, IgG levels were significantly higher in critical patients than moderate patients (z=-0.23; p>0.0,5, z=-3.60; p<0.05). There was no statistically significant difference in IgM titers between critical and severe patients. However, IgG titers were significantly higher in critical patients than in severe patients (z=-0.312; p>0.05, z=-4.300; p<0.05). Our study found that as disease severity increased, the patients' Nab titers also increased, which is consistent with previous literature. Based on the fundamental knowledge that the neutralizing activity of antibodies is the basis of humoral immunity and not the serologically detected antibody titer, it is reasonable to assume that the lack of an adequate response, or even a delayed response, in patients with severe disease may indicate a weakness in humoral immunity, potentially leading to severe and progressive disease. In addition, the extent to which these titers reflect the neutralizing function of the antibodies is still controversial and unclear; why these patients with high titers have severe disease when they are expected to be recovering is a topic of ongoing debate.

HT is the most common comorbidity associated with COVID-19 pneumonia and disease severity. It is one of the most important risk factors associated with mortality. In a study evaluating the immune response of infected and vaccinated healthcare workers, comorbidities such as HT, immunosuppression, autoimmune disease, and cardiac disease were associated with lower antibody responses (26). The incidence of HT in the population increases with age, and it is difficult to evaluate HT as an age-independent risk factor.

In our study, 76.3% of the patients had comorbidities, while 23.7% did not. The most common comorbidities were HT (57.5%), diabetes melitus (37%), cardiac diseases (coronary artery disease and congestive heart failure) (36.5%), pulmonary diseases (chronic obstructive pulmonary disease, asthma) (17.5%), chronic renal failure (7.5%) and cerebrovascular diseases (6.25%). There was no significant difference in IgM and IgG antibody titers between patients with comorbidities and those without comorbidities (z=-1.131; p>0.05, z=-0.334; p>0.05). This may be due to the low number of patients without comorbidities (19/80). However, when we examined the relationship between HT, the most common comorbidity, and antibody titers, patients with HT had significantly lower IgM antibody titers compared to those without HT (z=-2.044; p<0.05) similarly, the IgG titer of patients with HT was significantly lower than that of patients without HT (z=-7.611; p<0.05). This result is significant because it confirms that HT, a common comorbidity in COVID-19 patients, impairs the immune response.

The most commonly used biomarkers to determine the prognosis of the disease in COVID-19 are CRP, ferritin, D-dimer, fibrinogen, lymphocytes, procalcitonin, hemoglobin, platelet, and LDH. There are many studies

in which NLR, MLR and PLR have also been used to predict disease severity and mortality. These studies also investigated disease severity and found these values to be higher than reference values. There are studies showing that especially CRP, ferritin, D-dimer, and NLR values increase, and lymphocyte levels decrease as the severity of the disease increases (27-29).

The average values of CRP, ferritin, procalcitonin, D-dimer, and fibrinogen, as well as NLR and MLR, in our patients were higher than the reference values. Correlation analysis examined the relationship between biomarkers predictive of disease prognosis and Nab generated during the disease. Strong positive correlations were found between CRP, ferritin, platelets, D-dimer, NLR, MLR, PLR, and IgG antibody ($r=0.276$; $p<0.05$, $r=0.235$; $p<0.05$, $r=0.310$; $p<0.05$, $r=0.318$; $p<0.05$, $r=0.201$; $p<0.05$, $r=0.247$, $p<0.05$, $r=0.145$; $p<0.05$, respectively). No correlation was observed when performing the same analysis for IgM with all these biomarkers.

CONCLUSION

Previous research has established a direct correlation between disease severity and the presence and levels of Nab. Additionally, changes in biomarkers have been strongly linked to the severity of the disease. Our study's findings align with these existing studies, further supporting the correlation. This consistency may also be attributed to the fact that a significant portion of our study's participants experienced critical, to severe forms of the disease. Since the onset of the COVID-19 pandemic, numerous studies have explored demographic differences, disease severity, risk factors, comorbidities, and the relationship between the disease and both diagnostic laboratory parameters and immune response. Our results are in harmony with this body of literature. Moreover, our study is among the few that investigate the relationship between Nab generated during COVID-19 infection and prognostic biomarkers.

However, our study has certain limitations. All patients were hospitalized, and the majority were over 65 years old. testing was limited to a single serum sample taken on the 18th day following PCR positivity. Future studies with larger and more diverse populations, including both symptomatic and asymptomatic COVID-19 patients across different age groups, will be invaluable in assessing vaccine efficacy and the duration of protection offered by Nab.

ETHICS

Ethics Committee Approval: The study was approved The study was approved University of Health Sciences Hamidiye Scientific Research Ethics Board (decision no: 24/25, date: 09.07.2021).

Informed Consent: Written informed consent was obtained from patients to participate in this study. In accordance with the regulatory procedures of the study clinic, patients gave written informed consent for the processing and publication of their medical records (anonymized) for scientific purposes.

FOOTNOTES

Acknowledgment: This study was prepared from Ruveyda Alacahan Dürer's Ph.D. thesis conducted at the University of Health Sciences, Institute of Health Sciences.

Authorship Contributions

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

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

Financial Disclosure: This study was supported by the Scientific Research Projects Coordination Unit of the University of Health Sciences under project number 2021/162.

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):149-156
DOI: 10.4274/BMJ.galenos.2024.2023.3-18

Research

Evaluation of Orthopedic and Traumatology Diseases According to the 11th Revision of the International Classification of Diseases

Ortopedi ve Travmatoloji Hastalıklarının Uluslararası Hastalık Sınıflandırması 11. Revizyonuna Göre Değerlendirilmesi

Ahmet Yiğitbay

Siverek State Hospital, Clinic of Orthopedics and Traumatology, Şanlıurfa, Türkiye

ABSTRACT

Objective: International Classification of Diseases (ICD) codes provide valuable and detailed information to measure the quality, effectiveness, and safety of healthcare services. This paper addresses the key differences between ICD-10 and ICD-11 in relation to orthopedics and traumatology, focusing on the main challenges orthopedic physicians may face during the transition to ICD-11 and offering potential solutions to these issues.

Methods: This study outlines the main headings and diseases of the ICD-10 guidelines published by the World Health Organization and the ICD-11 guidelines published in 2019. The orthopedic and traumatology sections were compared.

Results: In ICD-10, chapter numbering is done with Roman numerals, whereas in ICD-11, Arabic numerals are used for chapter numbering. In ICD-11, the main code has 4 characters and the first two characters consist of letters, and the last two characters consist of numbers. The number of main headings, which was 21 in ICD-10, was updated to 26+2 in ICD-11. In ICD-11, unlike ICD-10, health services related to traditional medicine are included in the last sections, and these services have been tried to be standardized internationally. In addition, separate sections for the evaluation of functioning and additional codes were included in sections V and X.

Conclusion: When ICD-11 is analyzed in terms of its general structure, the number of disease diagnoses has increased and a more comprehensive hierarchical structure is observed compared with ICD-10. It is an absolute fact that physicians in particular will experience difficulties during the transition to ICD-11.

Keywords: Health management, health sciences, international classification of diseases, digitalization of health, orthopedics and traumatology diseases

ÖZ

Amaç: Uluslararası Hastalık Sınıflandırması (ICD) kodları, sağlık hizmetlerinin kalitesini, etkinliğini ve güvenliğini ölçmek için önemli ve ayrıntılı bilgiler sunmaktadır. Bu makalede, ICD-10 ile ICD-11 arasındaki ortopedi ve travmatolojiye yönelik temel farklar ele alınmış, ortopedi hekimlerinin ICD-11'e geçiş sürecinde karşılaşabilecekleri zorluklar ve bu sorunların nasıl çözülebileceği üzerinde durulmuştur.

Gereç ve Yöntem: Bu çalışmada Dünya Sağlık Örgütü tarafından yayınlanmış olan ICD-10 kılavuzu ile 2019 yılında yayınlanan ICD-11 kılavuzunun ana başlıkları ve hastalıkları ana hatları ile incelendi. Ortopedi ve travmatolojiyi ilgilendiren bölümler birbiri ile karşılaştırıldı.

Bulgular: ICD-10'da bölüm numaralandırılması Roma rakamları ile yapılırken, ICD-11'de bölüm numaralandırılması için Arapça rakamlar kullanılmıştır. ICD-11'de ana kod 4 karakterlidir ve ilk iki karakter harflerden, son iki karakter sayılardan oluşmaktadır. ICD-10'da 21 olan ana başlık sayısı ICD-11'de 26+2 olarak güncellenmiştir. ICD-11'de ICD-10'dan farklı olarak son kısımlarda geleneksel tıp ile ilgili sağlık hizmetlerine yer verilmiş ve bu hizmetler uluslararası standardize edilmeye çalışılmıştır. Ayrıca V ve X bölümlerde işleyiş değerlendirilmesi ve ek kodlar için ayrı bölümlere yer verilmiştir.

Sonuç: ICD-11'in genel yapısı incelendiğinde, hastalık tanılarının sayısında artış olduğu ve ICD-10'a kıyasla daha kapsamlı bir hiyerarşik yapıya sahip olduğu görülmektedir. ICD-11'e geçiş sürecinde özellikle hekimler tarafından zorluk yaşanacağı mutlak bir gerçektir.

Anahtar Kelimeler: Sağlık yönetimi, sağlık bilimleri, hastalıkların uluslararası sınıflandırılması, sağlığın dijitalleşmesi, ortopedi ve travmatoloji hastalıkları

Address for Correspondence: Ahmet Yiğitbay, Siverek State Hospital, Clinic of Orthopedics and Traumatology, Şanlıurfa, Türkiye
E-mail: ahmetyigitbay@gmail.com **ORCID ID:** orcid.org/0000-0002-7845-1974

Cite as: Yiğitbay A. Evaluation of orthopedic and traumatology diseases according to the 11th revision of the international classification of diseases. Med J Bakirkoy. 2025;21(2):149-156

Received: 01.05.2023
Accepted: 06.02.2024
Publication Date: 04.06.2025

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INTRODUCTION

Insurance companies, health information technology professionals, government agencies, and coders use the International Classification of Diseases (ICD) to properly record morbidity and mortality data, monitor epidemiological data, and help with medical reimbursement decisions. ICD codes provide useful and more detailed information for measuring the quality, effectiveness, and safety of healthcare services. The World Health Organization (WHO) publishes and contributes to the development of ICD codes (1). The WHO releases minor updates every year and major updates every 3 years. With each update that attempts to eliminate deficiencies, new codes provide more detailed information about the patient's condition. For example, while the right and left sides cannot be distinguished in patients with a distal radius fracture using ICD-9, this distinction can be made using ICD-10 codes. Similarly, volar or dorsal injury is not distinguished in a patient with a distal radius fracture in ICD-10, whereas volar and dorsal injuries are coded in two different ways in ICD-11.

WHO announced the 11th version of the ICD on its website and social media platform on June 18, 2018. Many diseases and disorders are included in ICD-11. In addition, signs and symptoms related to diseases, syndromes, injuries, external causes of illness, and death are also included in the new update. All codes in ICD-11 are presented in 26 main headings and two supplementary sections (V and X). Unlike ICD-10, health services related to traditional medicine were included in the latter sections, and these services were tried to be internationally standardized. In addition, separate sections are included for functioning assessment and extension codes in the supplementary sections V and X (2).

In this article, we aimed to evaluate the diseases related to the orthopedics and traumatology section in the ICD-11 guidelines and to help physicians initiate their transition to ICD-11.

METHODS

The study involved a comparison of ICD-10 and ICD-11 classifications, analyzing the changes introduced by the new classification system.

The research was conducted using literature review and document analysis methods. Data were obtained by examining the ICD-11 guidelines published by the WHO and official health coding systems. The differences between ICD-10 and ICD-11 were identified, with a particular focus on diagnostic and coding changes in the field of orthopedics and traumatology. Since no living organisms were used in this study, ethics committee approval was not required.

RESULTS

The main sections of ICD-10 and ICD-11 are presented in (Table 1). While chapter numbering in ICD-10 uses Roman numerals, Arabic numerals are used for chapter numbering in ICD-11. ICD-10 comprises 21 main headings and is generally classified according to parameters such as anatomical region and disease agent. The ICD-10 coding has 5 digits. The coding system employs an alphanumeric system that includes a letter in the first digit and a number in the other digits. The first step comprises the main heading, while the second and third steps contain the numbers formed by the combination of certain diseases. The fourth digit follows a decimal number and allows for more detailed disease coding. The fifth digit indicates a new disease or special condition. For example, for a patient with joint pain to be coded according to ICD-10, the main heading "diseases of the musculoskeletal system and connective tissue" should be selected, followed by the subheading of this section "other joint disorder, not elsewhere classified" with the letter "M" and the number "25". The fourth digit must then be selected. In the fourth step, an appropriate choice should be made. According to the ICD-10 classification, the code for joint pain is "M25.5." In special cases, a fifth level can be added (2).

ICD-11 is being developed within an interactive and constantly updating beta draft system (3). The number of main headings, which was 21 in ICD-10, was updated to 26+2 in ICD-11. The main heading of "diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism" in ICD-10 is divided into two main headings as "diseases of the blood or blood-forming organs" and "diseases of the immune system" in ICD-11. The main heading of "mental and behavioral disorders" in ICD-10 is divided into three main headings in ICD-11 as "mental, behavioral, or neurodevelopmental disorders", "sleep-wake disorders" and "conditions related to sexual health." In case of the emergence of new diseases, a section on "Codes for special purposes" has been created in ICD-11. For diseases related to traditional medicine, the heading "supplementary chapter traditional medicine conditions-module I" has been created. To evaluate the cognition status of the patients, the heading "supplementary section for functioning assessment" was created. In addition, the heading of "extension codes" has been added to detail conditions such as the severity of the disease, the patient's state of consciousness, and cause of infection (2,3).

In ICD-11, the main code consists of 4 characters; the first two characters are letters and the last two are numbers. Adding a mandatory number in place of the third character prevents unwanted words from being written. A letter in place of the second character provides a clear distinction between ICD-11 and ICD-10 codes. Alphanumeric codes cover the range of 1A00.00 to ZZ9Z.ZZ. Codes starting with "X" indicate an extension code. The letters "O" and "I" have been omitted to avoid confusion with the numbers "0" and "1." The first character of the code is always related to the section. For sections 01 to 09, the first character is a number between 1 and 9, while for sections 10 to 26, the first character is a letter. The code range in a single section always has the same character in the first position. For example, 1A00 is a code in section 01, AA00 is a code in section 10, BA00 is in section 11, and CA00 is a code in section 12. The last letter Y is reserved for the category "other specified" and the last letter Z is reserved for the category "unspecified." For example, the coding for a first metacarpal basal fracture according to ICD-11 will be listed under the main section "injury, poisoning or certain other consequences of external causes" in the "injuries to the wrist or hand" subsection as a "first metacarpal fracture" using an NC prefix. In summary, the first metacarpal fracture is coded as NC53.2 according

Table 1. ICD-10 and ICD-11 main sections

ICD-10 main sections	ICD-11 main sections
I. Infectious and parasitic diseases	1. Certain infectious or parasitic diseases
II. Neoplasms	2. Neoplasms
III. Diseases in the blood and blood-forming organs and certain disorders involving the immune mechanism	3. Diseases of the blood and blood-forming organs
IV. Endocrine, nutritional, and metabolic diseases	4. Diseases of the immune system
V. Mental and behavioral disorders	5. Endocrine, nutritional, and metabolic diseases
VI. Diseases of the nervous system	6. Mental, behavioral, or neurodevelopmental disorders
VII. Diseases of the eye and adnexa	7. Sleep-wake disorders
VIII. Diseases of the ear and mastoid process	8. Diseases of the nervous system
IX. Diseases of the circulatory system	9. Diseases of the visual system
X. Diseases of the respiratory system	10. Diseases of the ear or mastoid process
XI. Diseases of the digestive system	11. Diseases of the circulatory system
XII. Diseases of the skin and subcutaneous tissue	12. Diseases of the respiratory system
XIII. Diseases of the musculoskeletal system and connective tissue	13. Diseases of the digestive system
XIV. Diseases of the genitourinary system	14. Skin diseases
XV. Pregnancy, childbirth, and puerperium	15. Diseases of the musculoskeletal system or connective tissue
XVI. Conditions originating in the perinatal period	16. Diseases of the genitourinary system
XVII. Congenital malformation, deformation, and chromosomal abnormalities	17. Conditions related to sexual health
XVIII. Symptoms, signs, and abnormal clinical and laboratory findings, not classified elsewhere	18. Pregnancy, childbirth, or puerperium
XIX. Injury, poisoning, and certain other consequences of external causes	19. Certain conditions originating in the perinatal period.
XX. External causes of morbidity and mortality	20. Developmental anomalies
XXI. Factors influencing health status and contact with health services	21. Symptoms, signs, or clinical findings not classified elsewhere
XXII. Codes for special purposes	22. Injury, poisoning, or certain other consequences of external causes
	23. External causes of morbidity and mortality
	24. Factors influencing health status or contact with health services
	25. Codes for special purposes
	26. Supplementary chapter: Traditional medicine conditions
	V. Supplementary section for functioning assessment
	X. Extension codes

ICD: The International Classification of Diseases

to ICD-11. In addition, if requested, the side of the fracture (right, left, bilateral, etc.), the subtype of the fracture (avulsion, compression, greenstick fracture, etc.), whether it is an open or closed fracture, joint involvement, the specific region of the fracture, and related conditions (beating, self-harm, ill-treatment, etc.) can also be coded (Figures 1, 2).

For certain diseases, it is important to define both the etiology and manifestation. This is particularly important in mortality coding. In ICD-10, a dagger symbol was placed next to the etiology codes, and a star symbol was placed next to the finding codes. The dagger and asterisk system has been removed in ICD-11, but the functionality of coding the etiology and manifestation remains. A number of former asterisk codes that were previously used to identify disease manifestations are now listed in Chapter 21 "symptoms, signs, or clinical findings, not elsewhere classified". A portion of the former asterisk codes also reside in the

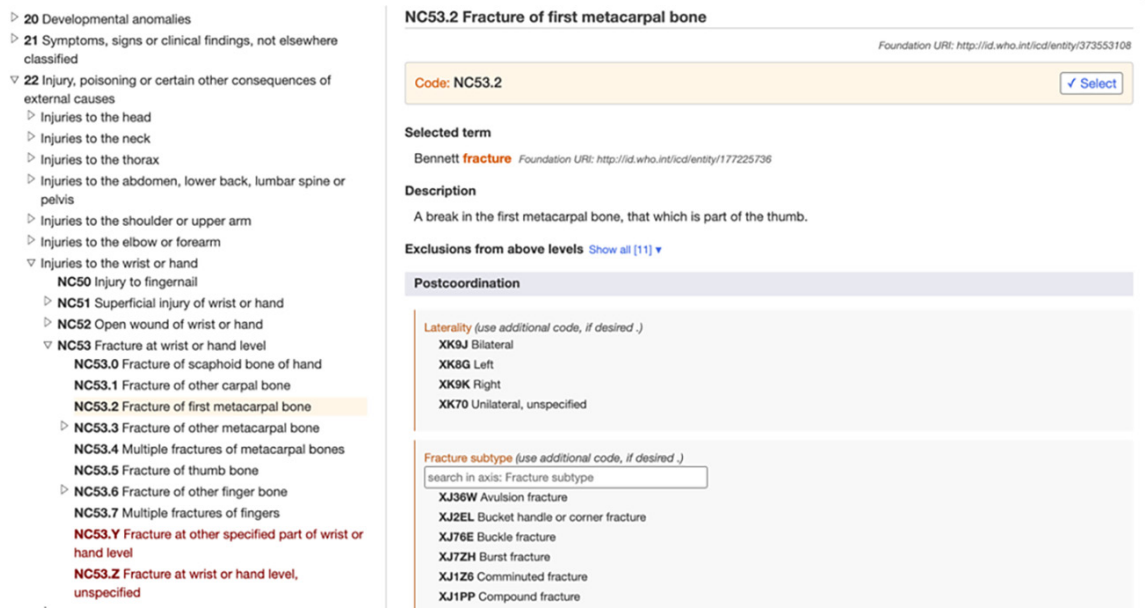


Figure 1. ICD-11 coding for first metacarpal fracture
ICD: The International Classification of Diseases

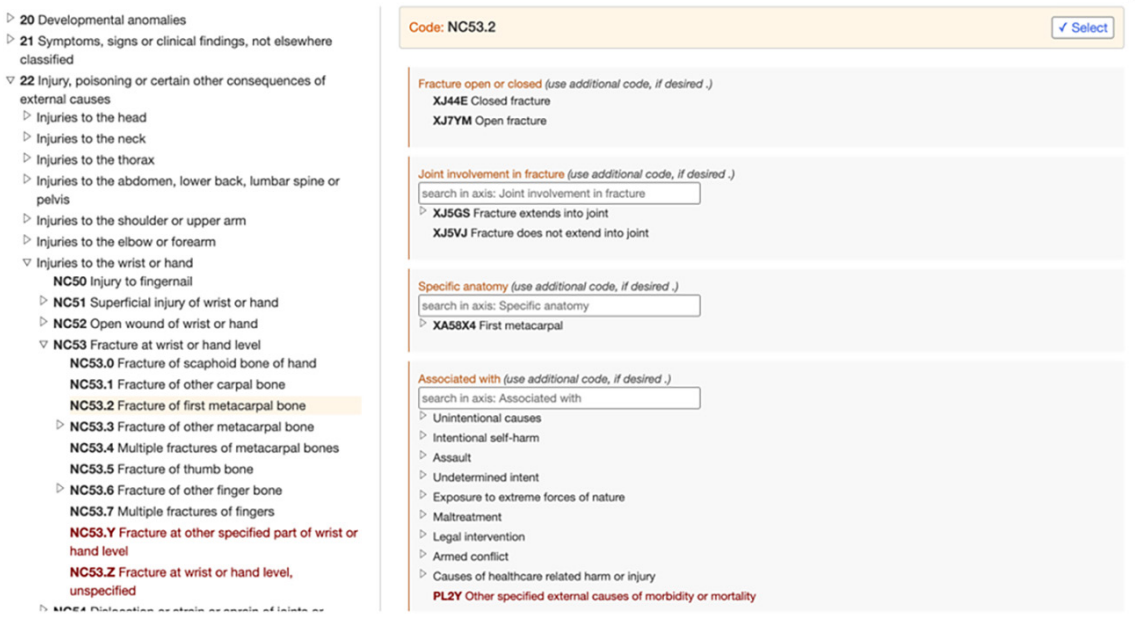


Figure 2. ICD-11 coding for first metacarpal fracture
ICD: The International Classification of Diseases

corresponding body system chapter. Asterisk codes that were repetitions of the dagger code were removed. Lists for coding optional anatomical details have been grouped into one section in Chapter X "extension codes" (2).

Topics concerning orthopedics and traumatology in ICD-11 are mainly "neoplasms" in Chapter 2, "diseases of the musculoskeletal system or connective tissue" in Chapter 15, "Developmental anomalies" in Chapter 20, "symptoms, signs or clinical findings, not elsewhere classified" in Chapter 21, and "injury, poisoning or certain other consequences of external causes" in Chapter 22 (2).

The "neoplasms" section in ICD-11 was created to code diseases of abnormal or uncontrolled cell proliferation that are not coordinated with an organism's requirements for normal tissue growth, change, or repair. For example, the ICD-11 diagnostic code for multiple myeloma is 2A83.1, and the coding scheme is shown in (Figure 3). In addition, internal and external diagnoses are listed under the same tab. The same disease was coded as C90.0 in ICD-10 (Figure 4). Certain types of morphology previously included in Annex-A of ICD-10 are included in this section of ICD-11. In the orthopedics and traumatology sections, all hematopoietic and lymphoid tissues were grouped together, and "malignant mesenchymal neoplasms" were added as a new group. The differences between ICD-10 and ICD-11 in the "neoplasms" section are presented in (Table 2).

Chapter 15 of ICD-11 is entitled "Diseases of the musculoskeletal system or connective tissue." The "systemic connective tissue disorders" subsection in ICD-10 has been moved to the fourth section named "diseases of the immune system" in ICD-11. "Soft tissue disorders, unspecified," which is frequently referred to in orthopedics and traumatology outpatient clinics, is coded in this section. This diagnosis is coded as M79.9 in ICD-10 and FB6Z in ICD-11. The differences between Chapters 15 of ICD-10 and ICD-11 are presented in (Table 3).

Chapter 21 of ICD-11 was created to provide a definitive diagnosis for less defined conditions and symptoms in cases in which necessary studies were avoided. This section has been largely restructured using a top-level hierarchy. Some clinical forms previously included in other sections as star codes have been moved to this section under ICD-11. Unlike ICD-10, diseases related to orthopedics and traumatology are coded in more detail under the subheading of 'Symptoms, signs or clinical findings of the musculoskeletal system' in Chapter 21 of ICD-11. For example, the diagnosis of "clicking hip" is coded as "M24.8: Other specific joint derangements, not elsewhere classified" under the main title of "XIII." Diseases of the musculoskeletal system and connective tissue" in ICD-10, coded as "ME80: Clicking hip" in Section 21 in ICD-11. The differences between Chapters 21 of ICD-10 and ICD-11 are presented in (Table 4).

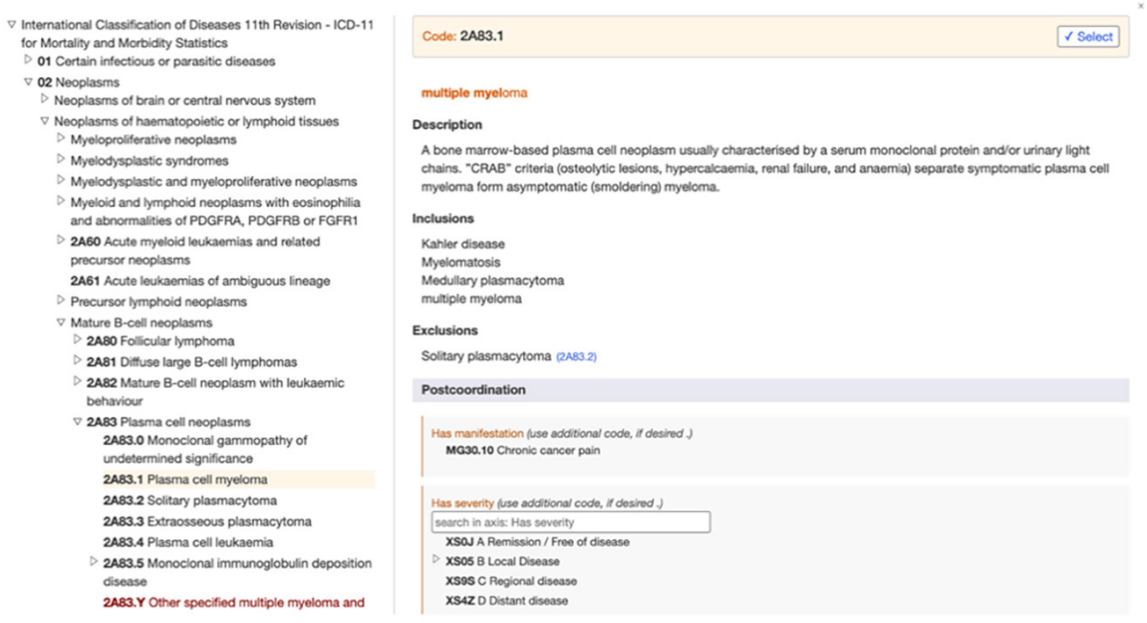


Figure 3. ICD-11 diagnostic code chart of multiple myeloma
ICD: The International Classification of Diseases

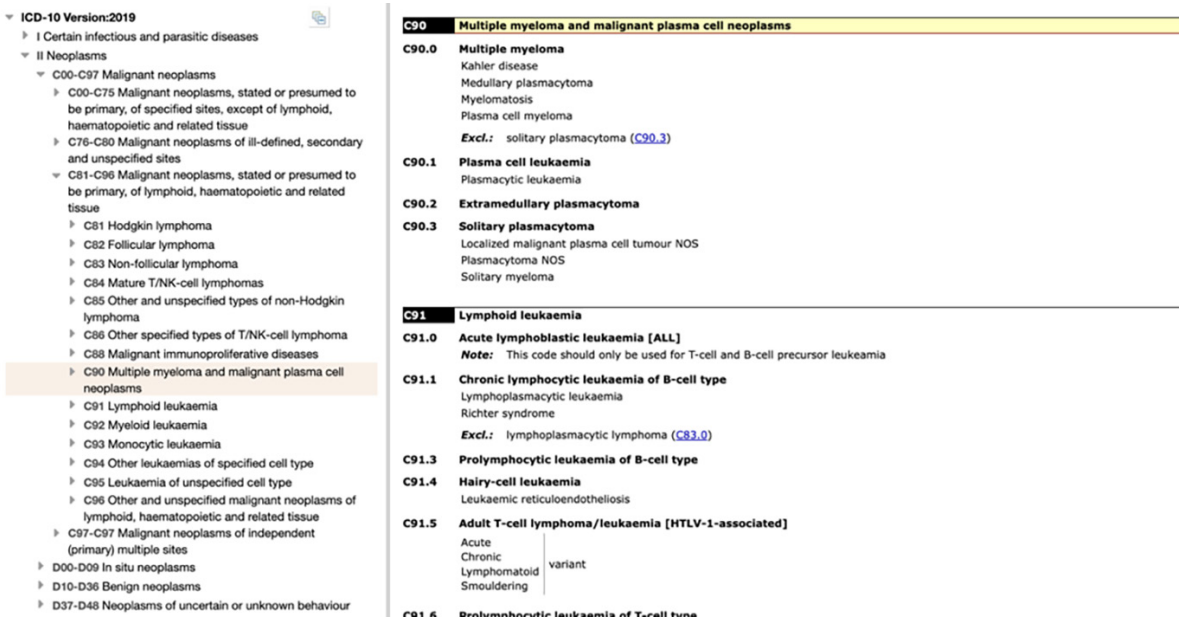


Figure 4. ICD-10 diagnostic code chart of multiple myeloma
ICD: The International Classification of Diseases

Table 2. Comparison of ICD-10 block structure with ICD-11 equivalent structure

ICD-10 block heading	ICD-11 equivalent structure
C00-C97 malignant neoplasms	Neoplasms of the brain or central nervous system Neoplasms in hematopoietic or lymphoid tissues malignant neoplasms, except for lymphoid, hematopoietic, central nervous system, or related tissues
D00-D09 *in situ* neoplasms	*In situ* neoplasms, except for lymphoid, hematopoietic, central nervous system, or related tissues
D10-D36 benign neoplasms	Benign neoplasms, except for lymphoid, hematopoietic, central nervous system, or related tissues
D37-D48 neoplasms with uncertain or unknown behavior	Neoplasms of uncertain behavior, except for lymphoid, hematopoietic, central nervous system, or related tissues Neoplasms of unknown pathology, except for lymphoid, hematopoietic, central nervous system, or related tissues

ICD: The International Classification of Diseases

Table 3. Comparison of ICD-10 block structure with ICD-11 equivalent structure

ICD-10 block heading	ICD-11 equivalent structure
M00-M25 Arthropathies	Arthropathies
M30-M36 systemic connective tissue disorders	Moved to Chapter 04 "diseases of the immune system"
M40-M54 dorsopathies	Conditions associated with the spine
M60-M79 soft tissue disorders	Soft tissue disorders
M80-M94 osteopathy and chondropathia	Osteopathy and chondropathia
M95-M99 other disorders of the musculoskeletal and connective tissue	Redistributed to various groupings, including certain specified acquired deformities of the musculoskeletal system or connective tissue, not elsewhere classified, and postprocedural musculoskeletal disorders, not elsewhere classified

ICD: The International Classification of Diseases

Table 4. Comparison of ICD-10 block structure with ICD-11 equivalent structure

ICD-10 block heading	ICD-11 equivalent structure
R00-R09 symptoms and signs involving the circulatory and respiratory systems	Split into two groups: Symptoms, signs, or clinical findings of the circulatory system; symptoms, signs, or clinical findings of the respiratory system
R10-R19 symptoms and signs involving the digestive system and abdomen	Symptoms, signs, and clinical findings of the digestive system or abdomen
R20-R23 symptoms and signs involving the skin and subcutaneous tissue	Split into two groups: Symptoms, signs, or clinical findings of the nervous system; symptoms, signs, or clinical findings of the musculoskeletal system
R30-R39 symptoms and signs involving the urinary system	Symptoms, signs, or clinical findings of the genitourinary system: Part of the grouping Symptoms, signs, or clinical findings of the genitourinary system
R40-R46 symptoms and signs involving cognition, perception, emotional state, and behavior	Reorganized into various subsections under mental or behavioral symptoms, signs or clinical findings
R47-R49 symptoms and signs involving speech and voice	Symptoms, signs, and clinical findings of speech and voice
R50-R69 general symptoms and signs	General symptoms, signs, and clinical findings
R70-R79 abnormal findings on blood examination without diagnosis	Included in the grouping symptoms, signs, or clinical findings of blood, blood-forming organs, or the immune system
R80-R82 abnormal findings on urine examination without diagnosis	Clinical findings on urine examination, without diagnosis under the grouping of symptoms, signs, or clinical findings involving the urinary system
R83-R89 abnormal findings on examination of other body fluids, substances, and tissues without diagnosis	Clinical findings in specimens from other specified organs, systems, and tissues under the general symptoms, signs, or clinical findings
R90-R94 abnormal findings on diagnostic imaging and in functional studies without diagnosis	Split into two subsections: Abnormal diagnostic imaging results not elsewhere classified; abnormal results of function studies of other organs and systems in the grouping abnormal results not elsewhere classified
R95-R99 Ill-defined and unknown causes of mortality	Ill-defined and unknown causes of mortality

ICD: The International Classification of Diseases

DISCUSSION

The ICD guideline is in wide use worldwide. It facilitates the recording, analysis and interpretation of mortality and morbidity data collected at different times in different countries and regions of the world. Thanks to this guideline, the archiving system and data collection processes are standardised and used in large studies. The resulting data provide critical information on the causes and consequences of diseases and deaths in the world.

Determination of causes of death and their grouping, evaluation of health services, archiving of records of cancer diseases, clinical research and evaluation of epidemiological studies can be done thanks to the ICD guideline.

As in all fields, it has become inevitable to analyze and document data on diseases and deaths in response to a certain code also in the field of health. Since ancient times, people have tried to statistically collect diseases and deaths in the field of health and archive them within the framework of certain rules. As a result of this archiving, the creation of the ICD guideline was inevitable (2,4).

Since the publication of the ICD-10 guidelines, there have been some changes in the subdivisions of the diagnoses and treatments of orthopaedic and traumatology diseases. As a result of these changes and due to the development of technology, the need for a new algorithm to classify diseases has arisen. When ICD-11 is analysed in terms of its general structure, it is seen that the number of disease diagnoses has increased and there is a more comprehensive hierarchical structure compared to ICD-10. In the coding of the diseases related to orthopaedics and traumatology department, while the main code according to ICD-10 is 3 digits, the main code according to ICD-11 is arranged as 4 digits. In ICD-10, some diseases related to the orthopaedics department could not be coded correctly. However, with ICD-11, it is seen that this has been eliminated in many diseases and a more detailed coding has been created in the classification of diseases. Nevertheless, although some deficiencies may arise in the future regarding the use of the ICD-11 guideline, these deficiencies will be eliminated with new updates (2).

One of the main objectives of ICD-11 is to classify diseases in a more standardised way and to carry this statistical data to the future in a more appropriate way. It is an absolute fact that especially physicians will experience difficulties during the transition to ICD-11. It is not yet known exactly when the health sysstem in Türkiye will switch to this new system.

The transition from ICD-10 to ICD-11 has introduced significant structural and functional improvements, particularly in the classification of orthopedic and traumatology diseases. With an expanded and more detailed coding system, ICD-11 provides a more comprehensive framework for disease classification, addressing many of the limitations present in ICD-10. The increased number of disease categories, the improved hierarchical structure, and the integration of supplementary codes allow for more precise diagnosis and documentation.

CONCLUSION

Despite these advancements, the transition to ICD-11 presents challenges, particularly for physicians and healthcare professionals who need to adapt to the new coding system. The complexity of implementation, training requirements, and potential inconsistencies in early adoption may pose difficulties in daily clinical practice. However, as healthcare systems worldwide gradually integrate ICD-11, continuous updates and refinements will help streamline the process and enhance the accuracy of disease classification. Overall, ICD-11 represents a crucial step toward the digitalization and standardization of health information, contributing to more efficient health management and epidemiological research. Future updates and modifications will be essential to further optimize its use in orthopedics and traumatology.

ETHICS

Ethics Committee Approval: Since no living organisms were used in this study, ethics committee approval was not required.

Informed Consent: Since this study was not conducted on humans, patient consent was not required.

FOOTNOTES

Financial Disclosure: No financial support has been received for the preparation of this manuscript.

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):157-162
DOI: 10.4274/BMJ.galenos.2024.2024.2-12

Research

A Neurosurgical Perspective on Electric Scooter Accidents

Elektrikli Scooter Kazalarına Nöroşirürjikal Bakış: Klinik Tecrübemiz

Eylem Burcu Kahraman Özlü, Elçin Tuğçe Mutlu, Kaan Durmuş, Arif Tarkan Çalışaneller

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

ABSTRACT

Objective: Electric scooters (e-scooters) have become the preferred personal vehicles in the world because of their easy accessibility, fast and even environmentally friendly features. E-scooters started to be used in İstanbul for the first time in Türkiye in 2019 and became popular in other metropolitans over time. We started encountering injuries associated with the growing use of e-scooters at our clinic.

Methods: This retrospective study evaluated 242 patients who were admitted to the Emergency Department of University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital due to electric scooter accidents between January 2020 and May 2023 for neurosurgical pathologies.

Results: Among the 12 patients included in the study, 8 were male and 4 were female. The mean age was 26.6 years (14-50). It was determined that none of the participants used protective equipment (helmet, knee pad, etc.). According to the retrospective evaluation, two patients were followed up for mild head trauma, seven for moderate head trauma, and one for severe head trauma. One patient with severe head trauma required long hospital stay and repeated surgical intervention. One patient underwent conservative follow-up, and the other required surgery.

Conclusion: E-scooters are environmentally friendly and can accelerate transportation; however, using them without complying with protective equipment and traffic rules can cause severe trauma. Despite our limited number of patients, we monitored one patient with trauma progressing to severe morbidity. We believe that injuries related to e-scooters will be more frequent in neurosurgery emergency practice.

Keywords: Accident, brain surgery, neurotrauma, trauma

ÖZ

Amaç: Elektrikli scooter (e-scooter), şehir içi ulaşımda kolay ulaşılabilir, hızlı, ucuz ve hatta çevre dostu yapılarıyla dünyada ve Türkiye'de tercih edilen bir kişisel ulaşım aracı olarak karşımıza çıkmaktadır. Türkiye'de ilk defa 2019 yılında İstanbul'da kullanılmaya başlanan e-scooterlar, zaman içinde diğer büyük şehirlerde de kullanıma girdi. E-scooter'ların artan kullanımıyla birlikte ilişkili yaralanmalar da nöroşirürji klinik pratiğimizde karşımıza çıkmaya başladı.

Yöntem: Bu çalışmada Ocak 2020-Mayıs 2023 tarihleri arasında Sağlık Bilimleri Üniversitesi Haydarpaşa Numune Eğitim ve Araştırma Hastanesi Acil Servisine e-scooter kazası nedeniyle başvuran 242 olgu, nöroşirürjikal patolojiler için retrospektif olarak değerlendirildi.

Bulgular: Çalışmaya dahil edilen 12 olgunun 8'i erkek, 4'ü kadın idi. Ortalama yaş 26,6 yıl (14-50). Hiçbirinin koruyucu ekipman (kask, dizlik vb.) kullanmadığı öğrenildi. Retrospektif değerlendirmede 2 olgu hafif, 7 olgu orta, 1 olgu ağır kafa travması nedeni ile takip edildiği belirlendi. Ağır kafa travmalı 1 olgunun uzun hastane yatışı ve tekrarlayan cerrahi girişim ihtiyacı mevcuttu. Olguların 1'i konservatif izlemle takip edilirken, 1'inde cerrahi girişim ihtiyacı oldu.

Sonuç: Ulaşımı hızlandıran ve aynı zamanda çevre dostu e-scooter'ın koruyucu ekipman ve trafik kurallarına uymaksızın kullanımının ciddi travmalara neden olduğu görülmektedir. Biz de sınırlı sayıdaki olgularımıza rağmen bir olgunun ciddi morbidite ile giden travma ile takibini yaptık. Zaman içinde e-scooter ilişkili yaralanmaların nöroşirürji acil servis pratiğinde sıklığının artacağını düşünmekteyiz.

Anahtar Kelimeler: Kaza, beyin ameliyatı, nörotravma, travma

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

Cite as: Kahraman Özlü EB, Mutlu ET, Durmuş K, Çalışaneller AT. A neurosurgical perspective on electric scooter accidents. Med J Bakirkoy. 2025;21(2):157-162

***This study was presented as a poster presentation at the 36th Congress of the Turkish Neurosurgical Society held on April 27-30, 2023.**

Received: 28.02.2024
Accepted: 12.07.2024
Publication Date: 04.06.2025

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INTRODUCTION

The world's growing population, especially in metropolitan areas and the resulting traffic jams have increased the need for faster vehicles for transportation. Shared electric scooters (e-scooters) have rapidly spread in many urban centers around the world since their first use in Santa Monica, California in 2017 (1). E-scooters, which started to be used as a better alternative to other means of urban transportation, have recently emerged as fast, easy, and cheap vehicles that are also respectful to nature (1,2).

E-scooters, which were first used in İstanbul in 2019 for the first time in our country, have spread to other metropolitan areas in recent years. They have become a practical, fast, and cheap means of transportation available through applications downloaded to mobile phones. Fees are determined according to the duration of use, and the distance and destination can be selected by the driver. Following their introduction in Türkiye in 2019, the speed limit for e-scooters was 25 km/h and the legal age limit was 15, per the regulation published in the related law for the first time in 2021. The same speed limit and age limit apply as of 2024. Driver's licenses and protective equipment are not compulsory, according to the regulation. They are particularly popular among the young population, especially during rush hours when traffic is heavy and public transportation is crowded.

The increase in the daily use of e-scooters has led neurosurgeons to encounter relevant injuries at emergency and trauma clinics with increasing frequency over the years. Head traumas ranging from mild to severe and pathologies related to the spine are observed with considerable frequency. In our study, we aimed to evaluate patients who presented to our emergency department because of e-scooter injuries and were consulted by a neurosurgeon between 2020 and 2023 for neurosurgical traumatic pathologies based on their demographic and clinical characteristics.

METHODS

Approval for this study was obtained from the University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital at a meeting (date: 29.11.2022, number: E-62977267-771). Among the 242 patients admitted to the Emergency Department of University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital between January 2020 and May 2023 due to e-scooter injuries, patients hospitalized and followed up in the neurosurgery clinic were retrospectively evaluated based on the medical records. Treatment consent forms were obtained for all patients and are available in the patient files.

All patients included in the study underwent cranial computed tomography (CT) and full spinal CT imaging after presenting to the emergency department. Among the 242 patients evaluated, 12 patients with pathology detected on radiological imaging due to neurosurgical injury who were followed up as inpatients in our clinic were included in the study. No exclusion criteria were applied for patients.

Statistical Analysis

Statistical analyses of the study were performed using the arithmetic mean. During the study, patient information, including age, sex, use of protective equipment, neurosurgical pathologies, neurological examination results, need for surgery after admission, intensive care hospitalization, and neurological status at discharge, was evaluated retrospectively based on the patient files.

RESULTS

Among the 242 patients admitted to the emergency department of our hospital due to e-scooter-related accidents, 172 (71.07%) patients with suspected cranial and/or spinal trauma underwent cranial and whole spinal CT examinations per the trauma protocol, and 98 (56.9%) of these patients with suspected radiologic or clinical findings were consulted to neurosurgery. Twelve (12.2%) of the consulted patients were treated as inpatients at the neurosurgery clinic. Ten patients were followed up due to head trauma and 2 due to spinal injury. One patient with severe head trauma was operated on urgently after admission and was followed up in the intensive care unit for a long period after the surgery. The remaining patients were followed up at our clinic.

Among the 12 patients in the study, 8 were male, and 4 were female. The mean age was 26.6 years (14-50). All patients were users of e-scooters. None of the patients used protective equipment (helmet, knee pad, elbow pad, etc.). No use of alcohol or sedatives was detected in any patient. (Table 1).

Based on the retrospective evaluation, 10 patients were found to have head trauma. Two patients were followed up for mild, seven for moderate, and one for severe head trauma. Among the patients hospitalized in our clinic, only one had concomitant orthopaedic traumatic pathologies. The patient was treated by an orthopaedic and

traumatology physician. Plastic and reconstructive surgery was performed for four patients with maxillofacial traumatic pathologies. The remaining patients had isolated cranial or spinal trauma.

One patient with severe head trauma required long hospital stay and repeated surgical intervention. The patient whose hematoma was discharged by decompressive craniectomy due to acute subdural hemorrhage was transferred to our clinic after follow-up in the intensive care unit (Figure 1). The patient was transferred to the clinic for rehabilitation based on the stable course of his general condition. Non-obstructive hydrocephalus was detected in the examinations performed due to sleepiness and regression in neurological score. The patient was referred to our clinic and underwent ventriculoperitoneal shunt procedure (Figure 2). The patient was re-transferred to the rehabilitation department with the same neurological condition as before the development of hydrocephalus, Glasgow Coma Scale (GCS) 9, quadriparesis, and no verbal response.

Th 12 vertebrae corpus fracture was detected in a 27 year-old male patient who was followed up for spinal trauma (Figure 3). Following the thoracolumbar magnetic resonance imaging, the thoracolumbar injury classification system (TLICS) score of the patient was calculated as 1, and a decision was made on conservative follow-up. A 14 year-old female patient with spinal trauma developed L1 burst fracture, posterior spinal element fracture, and ligament injury during advanced examination. The TLICS score of the patient was 4, and surgery was decided in the early posttraumatic period with posterior segmental instrumentation. Both patients were discharged without neurological impairment.

All nine patients hospitalized for mild and moderate head trauma were observed to have GCS: 15, without any neuromotor deficit. Only two patients were diagnosed with mild head trauma due to cephalic hematoma alone. Patients without radiological progression on follow-up imaging were discharged uneventfully.

Table 1. Neurological status and epidemiological features of the cases

	Sex	Age	Trauma type	Pathology-neurological status
Case 1	M	26	Moderate	Right frontal sinus fracture, anterior skull base fracture-GCS: 15
Case 2	M	28	Moderate	Left temporal bone fracture+epidural Hematomaz-GCS:15
Case 3	M	32	Moderate	Pneumocephalus+nasal ve bilateral orbital fracture-GCS:15
Case 4	F	50	Moderate	SAH-GCS:15
Case 5	M	30	Moderate	Maxillofacial ve frontal sinus fracture-GCS:15
Case 6	F	18	Moderate	Left frontal bone fracture-GCS: 15
Case 7	M	24	Spinal	Th-12 Corpus fracture, anterior column-normal exam. - TLICS: 1
Case 8	M	23	Severe	Subdural hematoma+left temporal bone fracture- intubated, GCS: 5
Case 9	M	29	Mild	Cephalohematoma-GCS: 15
Case 10	M	23	Moderate	Left frontal sinus fracture-GCS: 15
Case 11	F	23	Mild	Cephalohematoma-GCS:15
Case 12	F	14	Spinal	L1 compression fracture-normal exam.-TLICS: 4

GCS: Glasgow coma scale, TLICS: Thoracolumbar injury Classification and severity scale, Th-12: Th 12 vertebrae, SAH: Subarachnoid hemorrhage

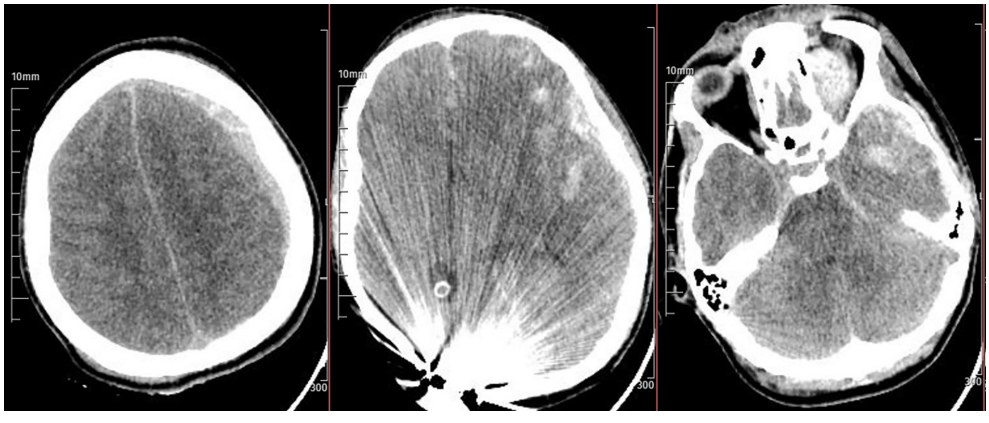


Figure 1. Severe head trauma patients preoperative CT images
CT: Computed tomography

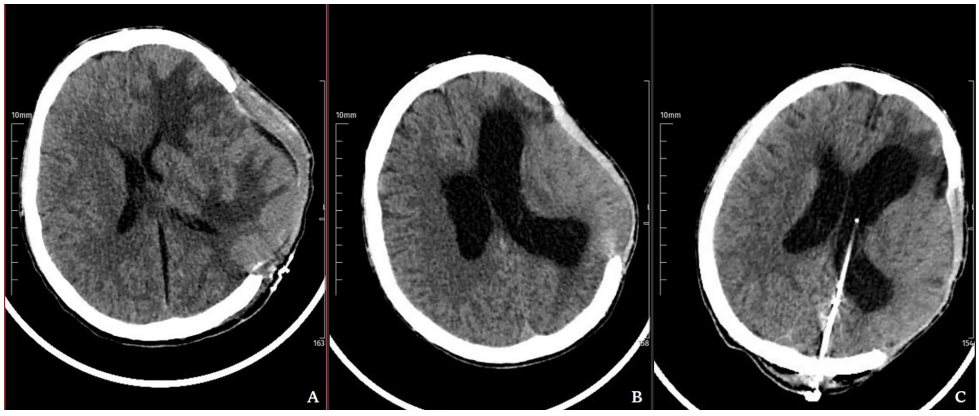


Figure 2. Severe head trauma patient A. Treatment of the subdural hematoma with decompressive craniectomy, postoperative B. Hydrocephalus in follow-up. C. After VP shunt surgery
VP: Ventriculoperitoneal

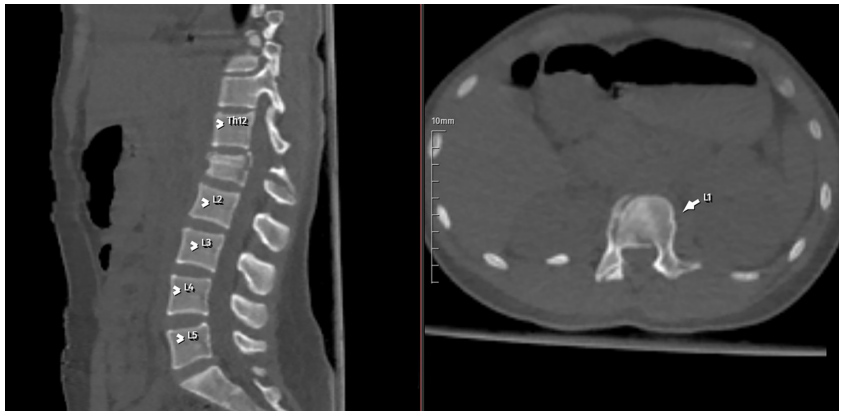


Figure 3. CT imaging of patient with L1 spine fracture after e-scooter injury
CT: Computed tomography, Th-12: Th 12 vertebrae

Seven patients were diagnosed with moderate head trauma due to bone and intracranial pathologies observed on cranial radiological imaging. One patient presented with traumatic subarachnoid hemorrhage, but no clinical symptoms. No worsening was observed during the clinical and radiological follow-up of the patient. Two patients had non-depressed fracture lines and thin epidural hemorrhage in the calvarium.

Signs of maxillofacial trauma accompanied by pneumocephalus were detected in four patients. All patients were referred by a plastic and reconstructive surgeon during hospitalization. Patients were referred to the polygenic risk scores outpatient clinic for elective treatment.

All patients with mild and moderate head trauma were discharged without neurological deficiency after clinical and radiological follow-up.

DISCUSSION

E-scooters are fast, easy, inexpensive, and environmentally friendly means of transportation where users can determine the destination and duration of their journey. It has become increasingly popular in Türkiye and around the world because of these reasons. The increasing frequency of this therapy brings with it the risk of serious morbidity and even mortality associated with high-speed trauma. Several studies have reported these risks, with rates of 115-250 injuries/million rides and 19 deaths/million rides (3-5). The most common e-scooter injuries were injuries to the upper extremity (54%), lower extremity (47%), head and neck (43%) (4).

Several studies in the literature reported that the frequency of young adult males in e-scooter accidents was significantly higher than that of females (4,6,7). Most patients present with mild head trauma. Long hospitalization periods, severe morbidity, and mortality were noted in patients with severe head trauma. The high proportion of male patients is noteworthy, especially among patients with severe trauma.

In the study of Kobayashi et al. (8) and Trivedi et al. (7), the use of alcohol and other drugs at varying frequencies was mentioned among the patients (2). In our study, the number of male patients was also significantly higher than the female patients. Despite the age and gender ratios being consistent with the literature, no alcohol or drug use was detected in any of our patients.

In the literature, extremity injuries are mentioned in most cases associated with e-scooters (4). In addition, other injuries causing long hospitalization periods, recurrent surgeries, and severe morbidity, such as severe head trauma, were also reported (9). Accordingly, using protective equipment becomes essential to reduce the risk of high-speed trauma injury associated with e-scooters. Many studies in the literature have mentioned the poor use of protective equipment when using e-scooters (7,8). E-scooter mobile applications contain expressions such as the use of protective equipment is recommended; however, this equipment cannot be supplied with the vehicle. This leads to the neglect of the use of protective equipment for e-scooters, which are alternatives to other means of transportation. None of our patients used protective equipment.

Spinal trauma associated with e-scooters were rarely mentioned in the literature. Injuries were mostly reported in relation to extremities or the head and neck region (9). A case report of Glynn et al. (5) presented a patient with cervical artery dissection who wore protective equipment. The clinical results were evaluated on the 5th day following the trauma. The patient who had no symptoms in the early posttraumatic period was significant in terms of the problems that may arise in the long term after the accident (5). Contrary to the common findings in the literature, a relatively high rate (16.6%) of patients with spinal trauma were detected in our series. One of these patients underwent surgery due to the need for surgical treatment. The findings suggested the importance of multidisciplinary and detailed evaluation of all patient systems after e-scooter accidents.

In Türkiye, membership is available to e-scooter applications used on cell phones with identity information and the condition of being over 15 years of age. Nevertheless, the fact that the 14 year-old patient who underwent surgery due to spinal trauma was using an e-scooter revealed insufficient supervision, suggesting that parents lacked sufficient awareness regarding this issue. The literature also mentions negligence regarding age, speed limits, and the use of protective equipment when using e-scooters.

We observed in our study that e-scooters, which are environmentally friendly, inexpensive, and fast vehicles, may cause mild or severe morbid outcomes without proper use. It was reported in the literature that using e-scooters without protective equipment and complying with traffic rules particularly caused severe trauma and even mortality (2). Despite our limited number of patients, we monitored one patient with trauma progressing to severe morbidity. The publications in the literature reported moderate head traumas caused by e-scooters in compliance with our series. We believe that patients should also be examined for spinal trauma. Proper regulations will enable safer use of e-scooters.

CONCLUSION

The fast and practical use of e-scooters in urban transportation and their environmentally friendly properties make them a prominent choice for transportation preferences. It should be noted that injuries resulting from neurosurgery can cause severe morbidity and even mortality. The injuries were associated with a significant deficiency correlated with the use of protective equipment. The importance of protective equipment, compliance with speed limits, and following traffic signs should be considered in terms of safety. Determining legal speed limits with traffic signs when using scooters, making it mandatory to have fixed protective equipment on shared scooters and building special roads for these vehicles may be a good way to protect against possible injuries.

ETHICS

Ethics Committee Approval: Approval for this study was obtained from the University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital at a meeting (dated 29.11.2022, number: E-62977267-771).

Informed Consent: Treatment consent forms were obtained for all patients and are available in the patient files.

FOOTNOTES

Authorship Contributions

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

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):163-171
DOI: 10.4274/BMJ.galenos.2024.2023.12-10

Research

The Effect of Low-intensity Resistance Training Combined with Blood Flow Restriction on Triceps Brachii Muscle Volume, Strength, and Performance

Kan Akımı Kısıtlaması ile Kombine Düşük Yoğunluklu Dirençli Egzersiz Eğitiminin Triceps Brachii Kas Hacmi, Kuvveti ve Performansına Etkisi

Yunus Emre Tütüneken[1,2], Emre Serdar Atalay[3], Yasemin Buran Çırak[2], Kadriye Öneş[4], Türker Şahinkaya[5], Bülent Bayraktar[5]

[1]University of Health Sciences Türkiye, Hamidiye Institute of Health Sciences, Department of Physiotherapy and Rehabilitation, İstanbul, Türkiye
[2]İstinye University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, İstinye University, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Gülhane Faculty of Physiotherapy and Rehabilitation, Department of Orthopedic Physiotherapy and Rehabilitation, Ankara, Türkiye
[4]University of Health Sciences Türkiye, İstanbul Physical Therapy Rehabilitation Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Türkiye
[5]İstanbul University, İstanbul Faculty of Medicine, Department of Sports Medicine, İstanbul, Türkiye

ABSTRACT

Objective: To compare the effects of low-intensity resistance training with blood flow restriction (LRT-BFR) and high-intensity resistance training (HI-RT) on triceps brachii muscle thickness and muscle strength, functional performance, and delayed-onset muscle soreness (DOMS).

Methods: Thirteen sedentary women performed two unilateral exercise protocols three days a week for six weeks. Participants were randomly divided into two groups according to exercise protocols. One group of participants performed LRT-BFR while the other performed HI-RT. The LRT-BFR group performed four sets [20-30% of 1 repetition maximum (1RM)]; and the HI-RT group performed three sets, 70-80% of 1RM. The two exercise protocols were performed in different sessions on the same day. Triceps brachii muscle thickness, triceps brachii, and biceps brachii muscle strength, upper extremity functional performance, and DOMS were evaluated before and after training.

Results: A statistically similar increase was observed in muscle thickness and strength ($60°xs^{-1}$), after exercise in both groups ($p<0.05$) but a greater increase in muscle strength ($180°xs^{-1}$) was obtained in the LRT-BFR group ($p<0.05$). There is no statistical difference between the groups for the upper-quarter Y balance test score and DOMS ($p<0.05$).

Conclusion: LRT-BFR had similar effects as HI-RT on muscle thickness and strength, functional performance, and DOMS. Where HI-RT cannot be used, we LRT-BFR is a viable alternative.

Keywords: Blood flow restriction, delayed onset muscle soreness, muscle strength, resistance exercise training, sedentary

ÖZ

Amaç: Bu çalışmanın amacı, kan akımı kısıtlamalı düşük yoğunluklu direnç eğitimi (KAK-DYDE) ile yüksek yoğunluklu direnç eğitiminin (YYDE) triceps brachii kas kalınlığı ve kuvveti, fonksiyonel performans ve gecikmiş başlangıçlı kas ağrısı (GKA) üzerine etkilerini karşılaştırmaktır.

Gereç ve Yöntem: On üç sedanter kadın, 6 hafta boyunca haftada 3 gün, iki farklı egzersiz protokolünü tek taraflı olarak uyguladı. Katılımcıların kolları egzersiz protokollerine göre rastgele iki gruba ayrıldı. Katılımcılar bir kolu ile KAK-DYDE gerçekleştirirken diğer kolu YYDE gerçekleştirdi. KAK-DYDE grubu 1 maksimum tekrarın %20-30'u (1RM) olmak üzere dört set; YYDE grubu 1RM'nin %70-80'i olmak üzere üç set olarak egzersizi uyguladı. İki egzersiz protokolü aynı gün farklı seanslarda gerçekleştirildi. Triceps brachii kas kalınlığı, triceps brachii ve biceps brachii kas kuvveti, üst ekstremite fonksiyonel performansı ve GKA eğitim öncesi ve sonrası değerlendirildi.

Address for Correspondence: Yunus Emre Tütüneken MD, İstinye University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, İstanbul, Türkiye
E-mail: emre.tutuneken@gmail.com **ORCID ID:** orcid.org/0000-0003-4080-5105

Cite as: Tütüneken YE, Atalay ES, Buran Çırak Y, Öneş K, Şahinkaya T, Bayraktar B. The effect of low-intensity resistance training combined with blood flow restriction on triceps brachii muscle volume, strength, and performance. Med J Bakirkoy. 2025;21(2):163-171

Received: 20.12.2023
Accepted: 16.07.2024
Publication Date: 04.06.2025

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ÖZ

Bulgular: Her iki grupta da egzersiz sonrası kas kalınlığında ve kuvvetinde ($60°xs^{-1}$) istatistiksel olarak benzer artış gözlendi ($p<0,05$), ancak KAK-DYDE grubunda kas dayanıklılığında ($180°xs^{-1}$) daha fazla artış elde edildi ($p<0,05$). Üst ekstremite Y denge testi puanı ve GKA açısından gruplar arasında istatistiksel anlamlı fark yoktur ($p<0,05$).

Sonuç: KAK-DYDE'nin kas kalınlığı ve kuvveti, fonksiyonel performans ve GKA üzerinde YYDE ile benzer etkilere sahip olduğunu bulduk. YYDE'nin kullanılamadığı durumlarda KAK-DYDE'nin alternatif olduğuna inanıyoruz.

Anahtar Kelimeler: Kan akımı kısıtlaması, gecikmiş başlangıçlı kas ağrısı, kas kuvveti, dirençli egzersiz eğitimi, sedanter

INTRODUCTION

Resistance training (RT) increases muscle strength and hypertrophy (1). These gains can positively impact daily physical functioning and significantly improve health, wellness, and sports performance (2).

The manipulation of RT variables such as frequency, rest interval, volume, and intensity are essential strategies to maximize exercise-induced muscular adaptations (3). Relating to intensity, RT with loads equating to 60-80% of maximum dynamic strength (1RM) has been recommended to achieve the greatest strength and muscle mass improvement (4). High-intensity resistance training (HI-RT) performed without proper supervision to achieve muscle adaptations may be impractical and dangerous (5).

In physically inactive individuals, HI-RT may increase the risk of injury and cause unusual exercise-induced pain, muscle soreness, and musculoskeletal injury (6). One study showed that HI-RT decreased central arterial compliance (7). Low arterial compliance increases the risk of coronary heart disease and systolic blood pressure, while reducing arterial baroreflex sensitivity (8,9). Thus, safe and effective methods should be developed to increase muscle volume and strength. Low-intensity RT with blood flow restriction (LRT-BFR) may be an alternative to HI-RT (10). Alternatively, when high-intensity activity is not feasible for sedentary individuals to maximize hypertrophy and strength, LRT-BFR can be used.

The literature reports conflicting results in studies comparing HI-RT and LRT-BFR. Several studies have shown that HI-RT promotes greater gain in muscle strength compared with LRT-BFR (5,10), but Takarada et al. (11) found that BFR training resulted in an increase in muscle strength comparable to HI-RT and showed significant increases in muscle hypertrophy. Yasuda et al. (5) and Vechin et al. (10) demonstrated that both HI-RT and LRT-BFR training induce increased muscle size. Meanwhile, studies investigating the effect of RT-BFR on delayed onset muscle soreness (DOMS) remain scarce; and while there are studies in the literature evaluating the immediate effects of LRT-BFR on DOMS, no long-term follow-up studies have been found. Alvarez et al. (12) found higher DOMS in LRT-BFR than in HI-RT. Another study reported the opposite result (13). Finally, no study has investigated the effects of LRT-BFR on upper limb functional performance.

This study compared the effects of LRT-BFR and HRT on triceps brachii muscle thickness (MT), strength, functional performance, and DOMS in young sedentary women.

METHODS

A prospective, randomized, controlled, single-blind study was conducted. To compare the effects of LRT-BFR and traditional RT on triceps brachii muscle strength, thickness, functional performance, and DOMS, a within-participants design was adopted. One arm of each participant (dominant or non-dominant) performed the exercise with cuff occlusion, while the other arm performed the exercise without occlusion. The arm condition of participants (with or without cuff occlusion) was randomized using a table created by a web-based computer program.

Triceps brachii MT [assessed by ultrasound (US)], muscle strength (assessed by isokinetic dynamometer), and functional performance [assessed by the upper quarter Y-balance test (the UQYBT)] were evaluated before the training program (Pre) and after the 6-week training period (Post) (Figure 1). DOMS was assessed after each training session. The Physical Activity Readiness Questionnaire for Everyone suggested by the American College of Sports Medicine was used for each participant's health screening before exercise was initiated (14).

Thirteen sedentary young women (age, 25.15±1.95 years; height, 162.62±5.56 cm; weight, 55.92±11.62 kg) were divided into the LRT-BFR and HI-RT groups (Figure 2). The number of arms was 26 (13 pairs).

The inclusion criteria were as follows: Eligibility to start an exercise program, normotension (blood pressure <135/85 mmHg), no tobacco use, and normal weight (body mass index <30 kg/m^2). The exclusion criteria included: Chronic disease (e.g., diabetes mellitus and uncontrolled hypertension), deep vein thrombosis, peripheral vascular disease, congenital heart disease, thromboembolism risk

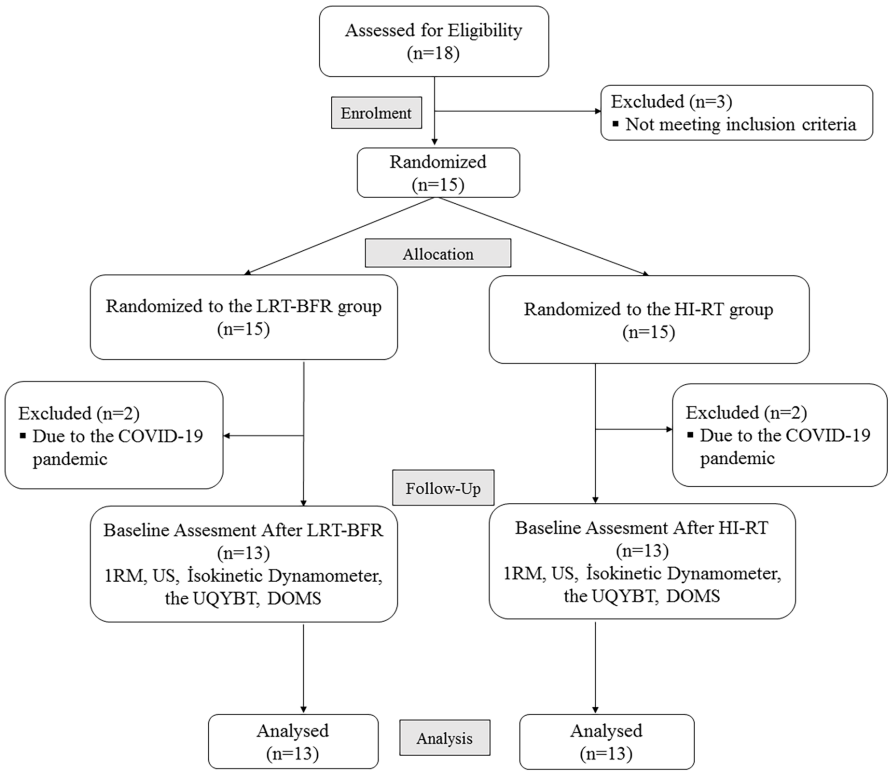


Figure 1. Study flowchart
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training, UQYBT: Upper quarter Y-balance test, US: Ultrasound, RM: Repetition maximum, DOMS: Delayed-onset muscle soreness

factors, history of orthopedic upper extremity surgery, and medication.

Ethical approval was obtained from the University of Health Sciences Türkiye, Hamidiye Non-Interventional Research Ethics Committee (decision number: 19/138, date: 08.11.2019). Participants were informed about the benefits and risks of the study before data collection began, and informed consent was obtained. The study was performed in accordance with the Declaration of Helsinki on good clinical practice.

All participants were familiarized with the strength testing and training apparatus before the commencement of the evaluation. Following a familiarization session, the participant's medical condition was screened. Both training groups performed a supervised free-weight elbow extension exercise 3 days/week for 6 weeks, and all participants performed strengthening exercise protocols unilaterally with the dominant and nondominant arm. In the LRT-BFR group, participants performed low-intensity exercises with 20-30% of 1RM and 75 repetitions unilaterally (4 sets of 30-15-15-15 repetitions, with 30-second of rest between sets) while wearing an elastic cuff to restrict blood flow at the most proximal arm region. The HI-RT group completed the high-intensity exercise with 70-80% of 1RM and 30 repetitions

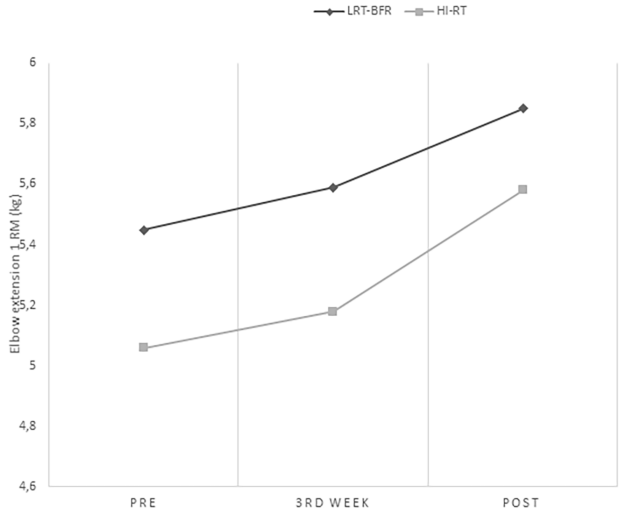


Figure 2. Muscle thickness (MT) of the triceps brachii after a 6-week training period. Data are presented as the mean ± standard deviation
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training, RM: Repetition maximum

3 sets of 10 repetitions, with 2-3 minutes of rest between sets (5). The "triceps extension-hand behind head" exercise with a dumbbell was used as the resistance exercise in this study. Participants stood with their feet shoulder width



Figure 3. Triceps extension resistance exercise

apart. They held a dumbbell behind their necks (Figure 3). Each participant was then instructed to extend their elbow concentrically (for 2-second), and then eccentrically (for 2-second) (15).

Before the training period, the BFR pressure was determined. After 15 min of rest in the seated position, an 8-cm-wide cuff was placed at the most proximal arm region and inflated until pulse absence was observed through auscultation with a vascular Doppler probe [Sonoline B cep doppler (8 Mhz)] over the radial artery. The occlusion pressure was adjusted to 70% of the maximum radial artery pressure throughout the BFR training session. The restriction pressure was determined based on previous studies (16,17). The participants did not complain of any discomfort or pain during the training.

1RM strength of elbow extension was assessed using a free-weight. Brzycki's formula was used to predict (18). The 1RM strength was assessed before the onset of training and after the 3rd and 6th week of training to adjust the training load for the LRT-BFR and HI-RT exercise sessions.

The researcher measured the triceps brachii MT using B-mode US (Esaote mylab 70 XVISION, Genua, Italy) and a 7.5-MHz linear array transducer (Esaote MyLab™ ClassC®). The probe was placed mediolaterally and transversely on the muscle. After the US images were obtained, MT, defined as the distance from the adipose tissue-muscle interface of the triceps brachii interface, was measured. The examiner abstained from compressing the muscle during the measurements. Two measurements were performed at each region, and mean values were used. The length of the upper arm was defined as the distance between the scapula acromion and the humerus lateral epicondyle. After determining the proximal 70%, 60%, and 50% points along the upper arm length, the MT was measured in these areas (MT70, MT60, and MT50). The upper arm MT was performed while participants stood with their arms relaxed at their sides and their forearms pronated (15).

İsokinetic testing of the triceps brachii and biceps brachii muscles was conducted bilaterally at angular velocities of 60°xs^{-1} and 180°xs^{-1} using an isokinetic dynamometer (CSMI Cybex Humac Norm, USA) with standard elbow attachments. To minimize extraneous body movements, participants were positioned supine. The lateral epicondyle of the humerus was aligned to the dynamometer's lever arm's center of motion. The participant's measured arm was positioned in full extension parallel to the participant's sides, while the participant's hand on the remaining arm was placed on the chest. The forearm was pronated during the test. The elbow joint range of motion was maintained at 0°-150°. For the peak torque/body mass (Nm·kg^{-1}) assessment, participants performed 4 repetitions at 60°xs^{-1}. Without rest, participants performed 20 repetitions at 180°xs^{-1} for the measurement of total work.

The UQYBT was performed to assess the dynamic balance and stability of the upper limbs. A modified UQYBT kit produced using athletic tape was used. To determine the testing directions of the modified UQYBT kit, a line of tape was used to mark one line for the medial direction. The superolateral (SL) and inferolateral (IL) directions were determined 135° from the medial line. Participants first placed their dominant hand at the intersection of the directions and assumed a push-up position, then sequentially touched the furthest point in the medial, SL, and IL directions with their free hand. After three practice trials, the participants took 2 min to rest and completed 3 more trials for the record. The reached points were recorded and directions' average distances (measured in centimeters) were computed. There was a 15-s break between trials. The trial was renewed if the participant could not hold the position and used their free hand to touch the ground (19,20).

DOMS was assessed before exercise and 12 and 24 hours after exercise using a 10-cm visual analog scale (0 cm: No pain, 10 cm: A lot of pain) over 6 weeks. Participants marked their perceived pain on a scale after each exercise, and the researcher measured the distances between each mark (21).

Statistical Analysis

The SPSS 22.0 statistical package (SPSS Inc., USA) was used for all statistical analyses. Kolmogorov-Smirnov/Shapiro-Wilk test was used to investigate the normal distribution

of the continuous variables. Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as percentage (%) and the number of patients. The chi-square test was used to determine differences in nominal variables between groups. Between-group comparison used the Student's t-test for normally distributed data. For the within-group comparisons, a paired samples t-test was used. Mann-Whitney U/Wilcoxon tests were used for data that were not normally distributed. Repeated measures analysis of covariance for the interaction effect between group and time. The effect size of the difference between the groups' means was calculated using Cohen's d and classified as small effect (0.20≤d<0.50), medium effect (0.50≤d<0.80), and large effect (d≥0.80). P<0.05 was regarded as statistically significant (22).

The G*Power 3.0.10 software was used to calculate the sample size. Based on the medium effect size (0.50) and when the bidirectional hypothesis is established for F-tests-ANOVA: Repeated measures, between factors, we estimated that a sample size of 13 upper extremity in each group would have a power of 80% to detect differences between groups with 5% error.

RESULTS

1RM values for elbow extension were increased for both the LRT-BFR group (pre: 5.45±1.06 kg, post: 5.85±1.16 kg, p<0.001) and the HI-RT group (pre: 5.06±1.05 kg, post: 5.58±1.08 kg, p<0.001). Both groups showed similar increments in 1RM values for elbow extension from the pre-training, 3rd week and post-training tests.

Both groups showed significant changes in MT after training in all regions. The LRT-BFR group exhibited a significant difference in MT50 (p<0.01), MT60 (p<0.001) and MT70 (p<0.001). The HI-RT group exhibited significant differences in MT50 (p<0.01), MT60 (p<0.001) and MT70 (p<0.01). Overall, the increment in MT was similar between the groups (p>0.05) (Table 1 and Figure 4).

The change in extension and flexion muscle strength values (60°xs^{-1}) between the groups was similar (p>0.05).

Table 1. Comparison of muscle thickness between the groups

	LRT-BFR group (n=13)			HI-RT group (n=13)			Treatment affect p-value	Cohen's d
Muscle thickness (cm)	Pre mean±SD	Post mean±SD	Within group p-value	Pre mean±SD	Post mean±SD	Within group p-value		
MT50	11.36±2.96	13.90±4.26	**<0.01***	11.73±3.19	14.08±4.02	**<0.01***	0.835	0.544
MT60	15.55±4.20	18.46±5.04	**<0.001****	15.58±3.57	18.70±4.92	**<0.001****	0.829	0.608
MT70	17.97±4.45	21.25±5.20	**<0.001****	18.65±4.24	22.06±5.30	**<0.01***	0.898	0.622

*p<0.01; **p<0.001. Statistically significant values are given by.
cm: Centimeter, LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training, MT: Muscle thickness, SD: Standard deviation

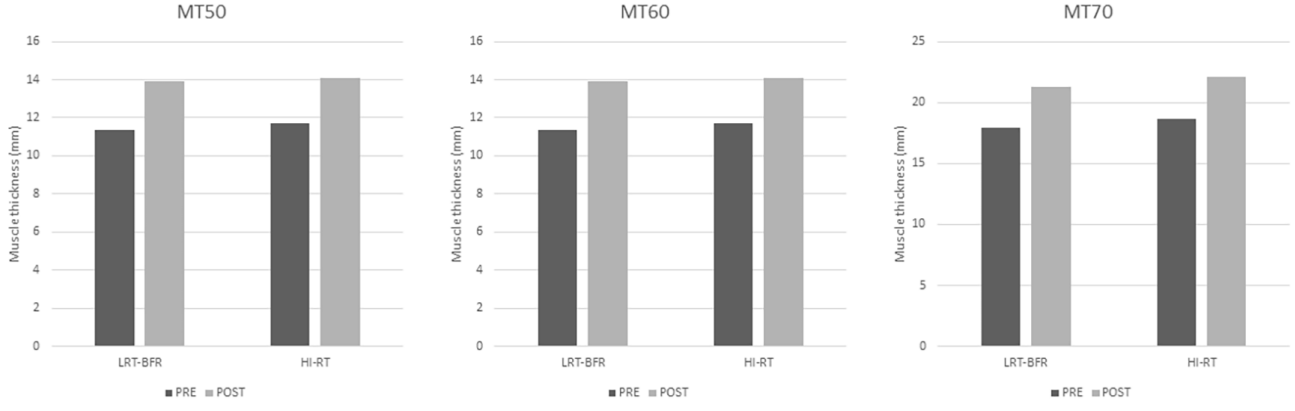


Figure 4. Muscle thickness (MT) of the triceps brachii after a 6-week training period. Data are presented as the mean ± standard deviation
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training, MT: Muscle thickness

Table 2. Comparison of muscle strength between the groups

	LRT-BFR group (n=13)		Mean difference 95% CI	Within group p-value	HI-RT Group (n=13)		Mean difference (CI) 95%	Within group p-value	Treatment affect p-value	Cohen's d
Peak torque (Nm·kg^{-1})	**Pre mean±SD**	**Post mean±SD**			**Pre mean±SD**	**Post mean±SD**				
Extension										
60°xs^{-1}	13.53±2.90	19.53±4.96	4.01-7.99	**<0.001****	14.15±3.60	20.23±4.38	3.76-8.37	**<0.001****	0.562	0.799
180°xs^{-1}	185.61±104.67	367.30±159.02	128.39-234.98	**<0.001****	218.23±113.23	353.53±182.98	65.31-205.28	**<0.001****	**<0.001****	0.699
Flexion										
60°xs^{-1}	16.07±2.39	21.07±3.66	3.22-6.78	**<0.001****	15.53±3.38	19.38±6.30	2.71-7.88	**0.090**	0.744	0.674
180°xs^{-1}	190.53±102.19	350.23±134.43	110.04-209.33	**<0.001****	214.07±118.23	374.61±158.67	95.47-225.58	**<0.001****	0.956	0.638

*p<0.05, **p<0.001. Statistically significant values are given by.
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training, CI: Confidence interval, Nm: Newton meter, SD: Standard deviation

However, the change in extension muscle strength values (180°xs^{-1}) was greater in the LRT-BFR group than in the HI-RT group (p<0.001) (Table 2).

Although significant differences were observed for the MR (LRT-BFR group's p<0.05; HI-RT group's p<0.01) and SLR (LRT-BFR group's p<0.01; HI-RT group's p<0.01), ILR (LRT-BFR group's p<0.01; HI-RT group's p<0.001), and composite score (LRT-BFR group's p<0.01; HI-RT group's p<0.001) on average, there were no significant differences for all directions and composite score between the groups after the training (Figure 5).

Before and after exercise, there was a significant reduction in DOMs in both groups (p<0.001). However, the changes in DOM values were not significantly different between the HI-RT and LRT-BFR group (p>0.05) (Figure 6).

DISCUSSION

Our study showed that LRT-BFR and HI-RT promoted increases in 1RM, with both protocols equally effective in inducing increases in triceps brachii muscle strength and thickness. However, differences in muscle endurance gains between the groups were associated with the LRT-BFR group. Upper limb functional performance increased in both groups. Both training protocols induced similar DOMS levels, although their magnitudes were low. Our study demonstrates LRT-BFR's effect on upper limb functional performance and, long term, DOMS. To the best of our knowledge, this is the first study to compare the effectiveness of LRT-BFR and HI-RT on upper limb functional performance and DOMS in young women.

Vechin et al. (10) found that both LRT-BFR and HI-RT were effective in increasing 1RM but stated that HI-RT training induced greater strength gains similarly. Yasuda et al. (5) reported that the change in 1RM strength was greater in the HI-RT group than in the LRT-BFR. We found that both the HI-RT and LRT-BFR groups showed improvements in elbow extension 1RM strength. Laurentino et al. (16) concluded that LRT-BFR was able to induce gains in 1RM like HI-RT. Our study showed that LRT-BFR training and HI-RT training produce similar increases in elbow extension 1RM strength.

Studies investigating the effects of BFR training on muscle hypertrophy are consistent. In a study comparing the effects of traditional RT and LRT-BFR, Korkmaz et al. (24) noted that MT increased more in the BFR group. Yasuda et al. (23) also observed BFR-induced increases in MT in a study utilizing the same intensity and duration of exercise. Another study by the same researcher reported muscle hypertrophy of similar magnitude achieved by HI-RT and LRT-BFR training

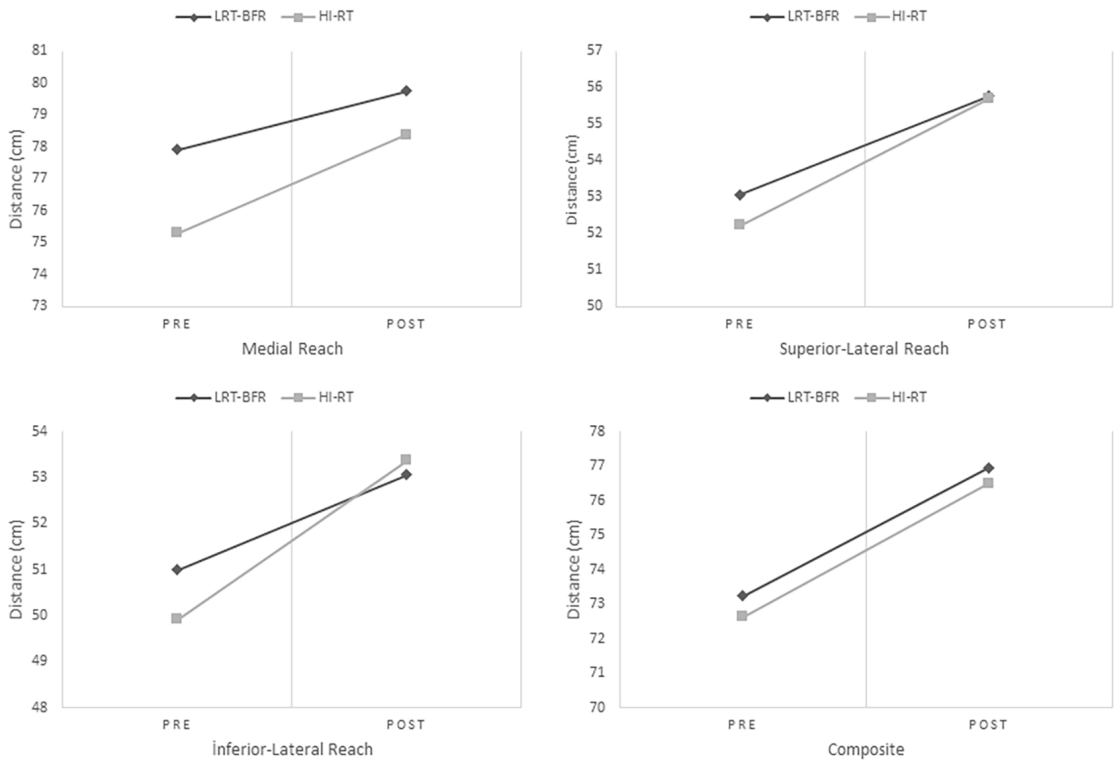


Figure 5. Comparison of the upper-quarter Y balance test (UQYBT) scores between LRT-BFR and HI-RT
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training

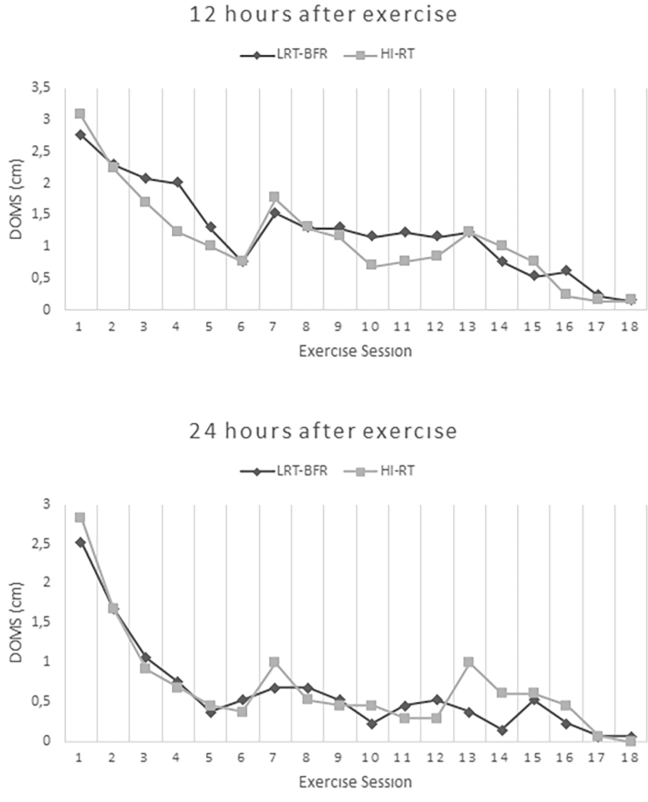


Figure 6. Delayed-onset muscle soreness (DOMS) 12 and 24 hours after resistance training
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training

(5). Our study showed that LRT-BFR produces a similar magnitude of MT increase as that reported in previous studies. Studies have reported that LRT-BFR and HI-RT muscle synthesis enhances muscle protein synthesis through the mTOR pathway (25,26). An increase in protein synthesis was detected even after a single session (5). These similar anabolic responses may induce similar increases in muscle hypertrophy in both the LI-BFR and control groups.

There are differences in the results of studies investigating the effect of BFR on strength. Most studies have reported that traditional RT causes greater increases in muscle strength. Yasuda et al. (5) demonstrated that HI-RT training induced greater improvements in elbow extension than LRT-BFR training. Another study investigating the long-term effects of LRT-BFR found that LRT-BFR was comparable to HI-RT in increasing elbow flexor muscle strength (11). Unlike several studies in the literature, Korkmaz et al. (24) found that LRT-BFR training increased muscle strength more than traditional RT. Our results showed that in the LRT-BFR group, triceps brachii muscle strength at an angular velocity of 60°xs^{-1} increase comparably to that in the HI-RT group. However, muscle strength improved more in the LRT-BFR group at an angular velocity of 180°s^{-1} than in the HI-RT group. Loads of 45-50% 1RM are required to increase the strength of untrained individuals (2). Thus, muscle strength changes due to LRT-BFR are thought to result from muscle hypertrophy, unlike HI-RT training (5).

Other than our study, no study on BFR training has investigated the effect of LI-BFR on upper extremity performance. Although BFR training is known to be an effective method for increasing muscle strength and volume, its effects on balance and postural control are unknown. Evaluating upper extremity performance using the UQYBT revealed no difference between limbs. However, there was improvement in all directions, and the total score increased for both limbs after training.

No study has investigated the effect of long-term LI-BFR on DOMS. Alvarez et al. (12) compared the effects of a single session of HI-RT and LI-BFR on muscle damage. They found that DOMS increased after LI-BFR. In their study, Wernbom et al. (13) reported that DOMS values were significantly greater in the non-occluded limb. Our results showed that both 6-week training protocols induced similar DOMS levels. DOMS values decreased as the sessions progressed in both groups. The results of DOMS studies in the literature are contradictory. The greater magnitude of DOMS in the occluded limb can be explained by the higher number of completed repetitions. Another underlying cause of the DOMS may be the ischemia-reperfusion and the formation of reactive oxygen species during exercise (27,28). In addition, the relatively high activation increase observed during eccentric phases can induce DOMS (13). The differences in the results of the studies may be due to differences in exercise volume, BFR pressure, cuff width, and limb type.

Study Limitations

That this study is controlled and randomized is one of its strengths. Another limitation of this study was that we used an individualized occlusion pressure prescription while applying BFR. Nevertheless, our study has limitations. First, our study group consists of sedentary young women; these effects should be investigated in different age groups and in women and men. Second, we did not use a pneumatic cuff system was not used, so that the occlusion pressure specific to the participant may not have been maintained during exercise.

CONCLUSION

We found that LRT-BFR had similar effects on improving muscle strength, muscle endurance, muscle volume, performance, and delayed onset muscle soreness compared to HI-RT. While muscle strength and endurance increased after both training sessions, a greater increase was obtained in the coronary artery calcification group. While similar increases were observed in muscle volume after both training sessions, this increase was similar in both groups. According to these results, we can say that RT-BFR was effective in inducing hypertrophy despite the low intensity. When we looked at the upper extremity performance evaluation results, we saw that the increase rate was similar in both training. When we compared the groups in terms of DOMS, the pain intensity after both exercise protocols was similar. In addition, the pain intensity decreased as the sessions progressed in both groups. Based on these results, we believe that LRT-BFR can be a suitable alternative in cases where HI-RT cannot be used.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Hamidiye Non-Interventional Research Ethics Committee (decision number: 19/138, date: 08.11.2019).

Informed Consent: Participants were informed about the benefits and risks of the study before data collection began, and informed consent was obtained.

FOOTNOTES

Authorship Contributions

Concept: Y.E.T., E.S.A., Y.B.Ç., Design: Y.E.T., E.S.A., Y.B.Ç., Data Collection or Processing: Y.E.T., E.S.A., K.Ö., T. Ş., Analysis or Interpretation: Y.B.Ç., Literature Search: Y.E.T., E.S.A., Writing: Y.E.T., E.S.A., Y.B.Ç., K.Ö., T. Ş., B.B.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):172-180
DOI: 10.4274/BMJ.galenos.2024.2024.8-12

Research

Association of IL6 with Laboratory Parameters, Obesity, and Osteoporosis in Turkish Geriatric Patients

Türk Yaşlı Hastalarda IL6 ile Laboratuvar Parametreleri, Obezite ve Osteoporoz Arasındaki İlişki

Deniz Yılmaz[1], Ezgi Şahin[2], Elif Ezirmik[3], Nilgün Işıksaçan[4], Faruk Karandere[1], Felemez Arslan[1]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
[2]İstanbul University, İstanbul Faculty of Medicine, Department of Internal Medicine, İstanbul, Türkiye
[3]İstanbul University, İstanbul Faculty of Medicine, Department of Public Health İstanbul, Türkiye
[4]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Biochemistry, İstanbul, Türkiye

ABSTRACT

Objective: The cytokine interleukin (IL)-6 is involved in the inflammatory response and has been linked to obesity and osteoporosis, which are public health issues in the geriatric population.

Methods: The study included 154 patients, 109 females and 45 males over the age of 65 without any complaints, who visited the internal medicine outpatient clinic at Bakırköy Dr. Sadi Konuk Training and Research Hospital. Femoral neck and lumbar L1-L4 vertebra bone densitometry was measured using dual-energy X-ray absorptiometry. Additionally, body mass index, arm and calf circumference, general laboratory parameters, and IL-6 levels were recorded.

Results: A positive correlation was found between IL-6 levels and monocyte and C-reactive protein (CRP) levels. Furthermore, a significant negative correlation was observed between IL-6 and albumin levels (p=0.002, p=0.000, p=0.005). However, no significant relationship was found between IL-6 levels and obesity or osteoporosis.

Conclusion: Results showed a significant positive correlation between IL-6 levels and monocyte and CRP levels and a significant negative correlation with albumin levels. However, no significant relationship was found between IL-6 levels and obesity or osteoporosis. Further studies are needed to fully explain the relationship between IL-6 and these health conditions fully.

Keywords: Interleukin-6, obesity, osteoporosis, inflammatory parameters, C-reactive protein

ÖZ

Amaç: Sitokin interleukin (IL)-6, enflamatuar yanıta dahil olmakta ve yaşlı nüfusta halk sağlığı sorunları olan obezite ve osteoporoz ile ilişkilendirilmektedir.

Gereç ve Yöntem: Çalışmaya, Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi iç hastalıkları polikliniğine başvuran, şikayeti olmayan 65 yaş üstü 109 kadın ve 45 erkek olmak üzere toplam 154 hasta dahil edilmiştir. Femur boynu ve L1-L4 lomber vertebra kemik yoğunlukları çift enerjili X-ışını absorpsiyometrisi ile ölçülmüştür. Ayrıca, vücut kitle indeksi, kol ve baldır çevresi, genel laboratuvar parametreleri ve IL-6 seviyeleri kaydedilmiştir.

Bulgular: IL-6 seviyeleri ile monosit ve C-reaktif protein (CRP) seviyeleri arasında pozitif bir korelasyon bulunmuştur. Ayrıca, IL-6 seviyeleri ile albümin seviyeleri arasında anlamlı bir negatif korelasyon gözlemlenmiştir (p=0,002, p=0,000, p=0,005). Bununla birlikte, IL-6 seviyeleri ile obezite veya osteoporoz arasında anlamlı bir ilişki saptanmamıştır.

Sonuç: Sonuçlar, IL-6 seviyeleri ile monosit ve CRP seviyeleri arasında anlamlı bir pozitif korelasyon ve albümin seviyeleri ile anlamlı bir negatif korelasyon olduğunu göstermiştir. Ancak, IL-6 seviyeleri ile obezite veya osteoporoz arasında anlamlı bir ilişki bulunamamıştır. IL-6 ve bu sağlık koşulları arasındaki ilişkiyi tam olarak açıklamak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Interleukin-6, obezite, osteoporoz, enflamatuar parametreler, C-reaktif protein

Address for Correspondence: Felemez Arslan MD, University of Health Science, Bakırkoy Dr. Sadi Konuk Training and Research Hospital
E-mail: feloarslan@gmail.com **ORCID ID:** orcid.org/0000-0001-8318-1860

Cite as: Yılmaz D, Şahin E, Ezirmik E, Işıksaçan N, Karandere F, Arslan F. Association of IL6 with laboratory parameters, obesity, and osteoporosis in Turkish geriatric patients. Med J Bakirkoy. 2025;21(2):172-180

Received: 25.08.2024
Accepted: 31.10.2024
Publication Date: 04.06.2025

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INTRODUCTION

Interleukin (IL)-6 is an essential cytokine involved in the systemic inflammatory response. IL-6 released from different cells is a critical stimulator in the hypothalamic-pituitary-adrenal axis and plays a notable role in the acute phase response. It is the leading procoagulant and proinflammatory cytokine. It effectively differentiates between B cells and processes or conditions such as inflammatory diseases, hematopoiesis, and oncogenesis (1-3).

The World Health Organization (WHO) defines the geriatric population as those aged 65 and over. As people age, even if they are completely healthy and functional, an increase in IL-6 and C-reactive protein (CRP) levels is observed, which is characterized by a mild pro-inflammatory state (4).

Malnutrition is defined as a condition caused by an imbalanced or insufficient diet, encompassing both undernutrition and overnutrition. In addition to cachexia and sarcopenia, obesity is included in the definition of malnutrition (5,6).

Obesity is a chronic inflammatory condition that causes an increase in inflammatory cytokines such as IL-6, tumour necrosis factor alpha (TNF alpha), and CRP. It is a substantial health problem that increases significantly in the older age group (7-9).

Increased IL-6 can cause thrombocytosis in lung, gastrointestinal, ovarian, breast, and lymphoma cancer. Similarly, increased IL-6 may lead to granulocytosis in lung, gastrointestinal, ovarian, genitourinary, and non-Hodgkin lymphoma (10).

METHODS

A total of 154 patients from the senior population were included in the study. Patients admitted to the internal medicine outpatient clinic of Bakırköy Dr. Sadi Konuk Training and Research Hospital in 2022 for routine control without any complaints were evaluated prospectively. The ethics committee of the same hospital approved the study with the ethics committee number 2022/10-15. Informed consent was obtained from the patients before the study.

Body mass index (BMI) was calculated as weight/height squared. According to the criteria of the WHO, based on BMI, those between 0-18.4 kg/m^2 were as "thin", those between 18.5 and 24.9 kg/m^2 were "normal", those 25-29.9 kg/m^2 were "overweight", and those >30 kg/m^2 "obese" evaluated.

To evaluate osteoporosis, bone density of the femoral neck and L1-L4 lumbar vertebrae was measured using dual-energy X-ray (DEXA) absorptiometry. T-score ranges between -1 and 1 were considered "normal", between -1 and -2.5 were "osteopenic", and below -2.5 were considered "osteoporotic".

The calf circumference was measured from the widest part of the calf, and the upper arm circumference was measured based on the midpoint between the shoulder and elbow using a tape measure. In the upper middle arm circumference measurement in the non-dominant arm, values between 23.5 cm and 32 cm were "normal", <23.5 cm "low", and >32 cm "high". In the context of calf circumference measurement, below 31 cm was considered "low". A calf circumference of <31 cm was considered an indicator of malnutrition.

Comorbid diseases such as diabetes mellitus (DM), hypertension, congestive heart failure, chronic kidney damage, and medications used by all patients included in the study were recorded.

Patients with a diagnosis of Alzheimer's, dementia, Parkinson's, active infection, malignancy, and those with osteoporosis-related fractures at any time were excluded from the study.

Laboratory Analysis

Collected blood samples were separated to obtain serum within 2 hours and kept in a freezer at -80 degrees until analysis.

The serum IL-6 concentration was measured by the chemiluminescence-immunoassay method in the Roche USA analyzer, and the minimum measurable concentration was one pg/mL. In our hospital, all biochemistry examinations were performed on the Cobas 800 Roche ABD device, and hemogram examinations were performed on the Mindray Cal 8000 device.

Statistical Analysis

Descriptive statistics were presented with mean, standard deviation (SD), median, and minimum-maximum values for continuous data and numbers and percentages for categorical data. The conformity of continuous data to normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. In data that do not comply with the normal distribution, the Mann-Whitney U test was used to compare two groups, and the Kruskal-Wallis test was used to compare more than two groups. Spearman's correlation analysis was employed to evaluate the relationships between numerical variables. The study considered a statistical significance level of $p<0.05$. The IBM SPSS 21.0 package program was used for statistical analysis.

RESULTS

This study included 154 patients over the age of 65 who were admitted to the internal medicine outpatient clinic for routine control without any complaints. 70.8% (n=109) of the patients were female, and 29.2% (n=45) were male. The age range was between 65 and 89. The mean age was 71.56 (SD=5.11).

Of the patients, 47.4% (n=73) had DM; 66.9% (n=103) had hypertension; 14.9% (n=23) had coronary artery disease; 5.8% (n=9) had congestive heart failure; 3.2% (n=5) had chronic kidney damage; 1.3% (n=2) had cerebrovascular damage; and 11.7% (n=18) had hypothyroidism.

Among the patients, %37 (n=57) use angiotensin-converting enzyme inhibitor or angiotensin two receptor blocker, 14.3% (n=22) use beta-blocker, 15.6% (n=24) use calcium channel blocker, 13% (n=20) use acetylsalicylic acid, 2.6% (n=4) use alpha-blocker, 1.3% (n=2) use gliclazide, 36.4% (n=56) use metformin, 16.9% (n=26) use dipeptidyl peptidase four inhibitor, 5.8% (n=9) use sodium-glucose co-transporter 2 (SGLT2) inhibitor, 11% (n=17) use insulin, 8.4% (n=13) use levothyroxine, 3.2% (n=5) use selective serotonin reuptake inhibitor/serotonin (SSRI), norepinephrine reuptake inhibitor (SNRI), 24.7% (n=38) use proton pump inhibitor, 18.8% (n=29) use statin, 20.8% (n=32) use thiazide diuretic, 2.6% (n=4) use furosemide, 0% 6 (n=1) used spironolactone.

When body mass indices are evaluated, the average BMI is 29.01±4.63 kg/m^2. The mean arm circumference measured was 28.44 (SD=3.36) cm, and the mean calf circumference was 36.14 (SD=3.76) cm. A statistically significant, positive, and strong correlation was found between arm and calf circumference, r=0.666, p=0.000. A statistically significant positive and robust correlation was found between arm circumference and BMI (r=0.799) (p=0.000). A similarly substantial, positive, and strong correlation was found between calf circumference and BMI (r=0.655, p=0.000) (Table 1).

Considering the laboratory parameters, of the patients, mean glucose was 128.24 (SD=52.96) mg/dL, mean creatinine was 0.85 (SD=0.22) mg/dL, mean albumin was 4.6 (SD=0.34), mean protein was 7.23 (SD=0.44) g/dL, mean low-density lipoprotein (LDL) cholesterol was 118.03 (SD=39.82) mg/dL, mean high-density lipoproteins (HDL) cholesterol was 52.65 (SD=13.23) mg/dL, mean triglyceride was 148.06 (SD=76.31) mg/dL, mean transferrin was 3.45

Table 1. The relationship between IL-6 and biochemical parameters (Spearman correlation analysis was used r: correlation coefficient n: number of individuals)

		Calf circumference	IL- 6	BMI	Monocyte	Transferrin	Albumin	CRP
Arm circumference	r	0.666	0.095	0.799	-0.085	0.155	0.027	0.141
	p	0.000	0.242	0.000	0.294	0.055	0.738	0.082
	n	154	154	154	154	154	154	154
Calf circumference	r		0.079	0.655	-0.039	0.028	-0.058	0.110
	p		0.328	0.000	0.634	0.735	0.478	0.175
	n		154	154	154	154	154	154
IL-6 level	r			0.126	0.254	0.059	-0.227	0.586
	p			0.121	0.002	0.465	0.005	0.000
	n			154	154	154	154	154
BMI	r				-0.131	0.244	-0.048	0.175
	p				0.107	0.002	0.553	0.03
	n				154	154	154	154
Monocyte	r					-0.109	-0.090	0.382
	p					0.180	0.267	0.000
	n					154	154	154
Transferrin	r						0.072	0.046
	p						0.374	0.570
	n						154	154
Albumin	r							-0.172
	p							0.033
	n							154

IL: Interleukin, BMI: Body mass index, CRP: C-reactive protein

(SD=5.79) g/L, mean ferritin was 83.96 (SD=107.35) µg/ dL, mean vitamin B12 was 432.78 (SD=299.54), mean CRP was 5.39 (SD=9.94) mg/L, mean alanine transferase (ALT), was 17.46 (SD=9.67) U/L, mean aspartate transferase (AST) was 19.24 (SD=6.99) U/L, mean alkaline phosphatase (ALP) was 81.06 (SD=25.08) U/L, mean lactate dehydrogenase (LDH) was 192.07 (SD=40.12) U/L, mean total leukocyte count was 7455 (SD=2300)/mm^3, mean hemoglobin was 13.39 hematocrit was 42.78% (SD=32.45), mean neutrophil count (SD=1.60) g/dL, mean was 4550 (SD=1813)/mm^3, platelet count was 262805 (SD=75831)/mm^3, mean lymphocyte count was 2206 (SD=745.73)/mm^3, mean monocytes count was 468.18 (SD=149.80)/mm^3, mean parathyroid hormone was 55.29 (SD=31.77) pg/mL, mean vitamin D level was 20.33 (SD=11.27) µg/L, mean IL-6 level was 3.48 (SD=5.62) pg/mL.

There was a statistically significant, positive, and moderate correlation between IL-6 level and the number of monocytes (r=0.254) (p=0.002). A statistically significant negative and weak correlation was found between IL-6 and albumin levels (r=0.227, p=0.005). A statistically significant, positive, and strong correlation was found between IL-6 and CRP levels (r=0.586); (p=0.000). It was observed that there was a statistically significant, positive, and moderate correlation between the number of monocytes and the CRP level (r=0.382, p=0.000). A statistically significant negative and weak correlation was found between CRP and albumin levels (r=0.172, p=0.033). A weak but statistically significant positive correlation was found between BMI and CRP level (r=0.175) (p=0.030). A positive and weak but statistically significant correlation was found between BMI and transferrin level (r=0.244, p=0.002) (Table 1).

According to BMI, of the patients, 0.6% (n=1) were underweight, 21.4% (n=33) were normal weight, 35.7% (n=55) were overweight, and 42.2% (n=66) were obese. No statistically significant difference was found between the albumin, transferrin, CRP, monocytes, and IL-6 levels in obese and non-obese patients (Table 2).

When the relationship between obesity and other biochemical parameters was investigated, a statistically significant difference was observed in ALT, LDH, ALP, and lymphocyte levels between obese and non-obese patients. ALT, LDH, ALP, and lymphocyte levels were higher in obese patients. (respectively p=0.028; p=0.003; p=0.024; p=0.045) (Table 3).

When the correlation between the use of the drug and BMI, arm circumference, and calf circumference was analyzed, the mean arm circumference of the patients SSRI/SNRI users was 28.5 (SD=3.3) cm, SSRI/SNRI non-users were 25.2 (SD=3.4) cm. The arm circumference of the patients' SSRI/SNRI users was significantly higher than the non-users (p=0.042). No significant correlation was detected between the use of other drugs and the mean arm circumference. The mean calf circumference was 36 cm (SD=3.7) for SGLT2 users and 38.4 cm (SD=3.3) for SGLT2 non-users when the correlation with the mean calf circumference was investigated. The calf circumference of patients using SGLT2 inhibitors was significantly lower than that of SGLT2 non-users (p=0.038). No significant correlation was found between other drugs and calf circumference. The mean BMI of patients who were metformin users was 28.4 (SD=4.4) kg/m^2, and non-users were 30.2 (SD=4.8) kg/m^2. The metformin users had a significantly higher BMI (p=0.026). The patient SGLT2 users' mean BMI was 28.8 (SD=4.5) kg/m^2, and the non-users' mean BMI was 32.6 (SD=4.9) kg/m^2. The BMI of the patients who were SGLT2 non-users was significantly higher than that of the users (p=0.043). No relationship was detected between the use of other drugs and BMI (Table 4).

In the bone densitometry measured with DEXA, the patients' mean femoral neck measurement was -1.25 (SD=0.99), and the L1-L4 vertebra measurement was -0.92 (SD=1.47). Based on the lumbar measurements, 48.1% (n=74) of the patients were average, 34.4% (n=53) were osteopenic, and 17.5% (n=27) were osteoporotic.

Table 2. The relationship between IL-6 and obesity

	Not obese					Obese					Mann-Whitney U test	p-value
	Mean	Standard deviation	Median	Min.	Max.	Mean	Standard deviation	Median	Min.	Max.		
Albumin	4.60	0.40	4.65	2.50	5.32	4.60	0.24	4.61	4.00	5.19	2689.0	0.457
Transferrin	2.74	049	2.70	1.75	4.18	4.43	8.84	2.83	2.16	53.60	2409.5	0.077
CRP	5.68	11.99	2.00	0.00	96.00	4.99	6.19	2.00	0.52	31.00	2546.0	0.199
Monocyte	478.65	146.37	470.00	230.00	970.00	453.85	154.35	420.00	210.00	910.00	2573.0	0.242
IL-6	3.83	6.97	1.30	1.00	56.25	3.01	2.86	1.99	1.00	16.11	2643.5	0.353

IL: Interleukin, CRP: C-reactive protein, Min.: Minimum, Max.: Maximum

Table 3. The relationship between obesity and biochemical parameters

	Not Obese					Obese					Mann-Whitney U test	p-value
	Mean	Standard deviation	Median	Min	Max	Mean	Standard deviation	Median	Min.	Max.		
Glucose	122.76	47.68	106.00	75.20	309.00	135.73	58.99	117.40	84.50	399.00	2385.0	0.063
Urea	36.40	10.93	35.60	18.50	67.80	34.94	10.88	32.40	16.00	58.00	2667.5	0.410
Creatine	0.85	0.23	0.82	0.43	1.53	0.83	0.21	0.80	0.48	1.43	2775.5	0.669
AST	19.21	6.89	17.50	11.00	56.80	19.28	7.17	18.20	8.20	45.40	2855.5	0.892
ALT	15.98	7.91	13.90	8.20	52.30	19.50	11.42	15.60	9.10	68.00	2293.0	0.028
LDH	184.35	33.01	180.00	126.00	292.00	202.65	46.40	203.00	126.00	426.00	2093.5	0.03
ALP	77.87	25.15	76.00	13.00	172.00	85.45	24.49	82.00	35.00	156.00	2274.0	0.024
Protein	7.21	0.43	7.21	6.20	8.65	7.25	0.45	7.23	6.41	8.66	2782.0	0.686
Albumin	4.60	0.40	4.65	2.50	5.32	4.60	0.24	4.61	4.00	5.19	2689.0	0.457
LDL	116.64	40.55	109.80	54.40	255.20	119.94	39.03	121.20	44.60	220.70	2658.5	0.392
HDL	53.11	13.58	52.30	28.00	85.50	52.02	12.83	51.00	27.00	85.40	2835.5	0.835
TG	140.77	76.57	122.00	45.00	449.00	158.05	75.38	140.00	45.00	456.00	2403.5	0.074
Transferrin	2.74	0.49	2.70	1.75	4.18	4.43	8.84	2.83	2.16	53.60	2409.5	0.077
Ferritin	93.37	120.53	57.30	8.60	800.00	71.06	85.33	51.90	8.80	639.00	2637.5	0.351
Vit B12	448.36	302.02	376.00	111.00	2000.00	411.45	297.12	321.00	100.00	1621.00	2510.0	0.162
CRP	5.68	11.99	2.00	0.00	96.00	4.99	6.19	2.00	0.52	31.00	2546.0	0.199
IL-6	3.83	6.97	1.30	1.00	56.25	3.01	2.86	1.99	1.00	16.11	2643.5	0.353
WBC	7509.89	2210.36	7140.0	3040.00	13970.00	7381.38	2434.34	6710.00	2900.00	13900.00	2593.0	0.273
HGB	13.50	1.61	13.60	6.20	16.40	13.25	1.60	13.30	8.60	17.00	2573.0	0.242
HTC	44.88	42.51	40.60	20.20	439.00	39.90	4.21	40.50	28.40	49.10	2615.5	0.311
PLT	260640.45	74502.17	257000.00	850000.00	447000.00	265769.23	78099.65	255000.00	137000.00	506000.00	2884.0	0.975
NEU	4727.30	1816.91	4320.00	1600.00	10270.00	4308.31	1794.23	3830.00	1420.00	10340.00	2396.0	0.069
LYM	2081.57	623.91	2060.00	940.00	4070.00	2377.08	861.95	2200.00	1040.00	4970.00	2343.5	0.045
Monocyte	478.65	146.37	470.00	230.0 0	970.00	453.85	154.35	420.00	210.00	910.00	2573.0	0.242
PTH	53.79	35.18	46.05	18.45	273.90	57.34	26.53	53.67	17.78	146.00	2454.5	0.109
D-vit	20.65	11.28	19.40	3.00	53.50	19.88	11.33	18.50	5.70	74.30	2737.5	0.571

AST: Aspartate transferase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase, ALP: Alkaline phosphatase, LDL: Low-density lipoprotein, HDL: High-density lipoproteins, TG: Thyroglobulin, CRP: C-reactive protein, WBC: White blood count, HGB: Hemoglobin, HTC: Hydrothermal carbonization, PLT : Platelet count, NEU: Neutrophils, LYM: Lymphocytes, PTH: Parathyroid hormone

Table 4. Correlation between drugs used and mean arm circumference, calf circumference, and BMI (Mann-Whitney U test was used)

	N		Arm Circumference						Calf Circumference						BKI					
			Mean	Std. Dev	Median	Min	Max	p	Mean	Std. Dev.	Median	Min	Max	p-value	Mean	Std. Dev.	Median	Min	Max	p
ACE/ARB	NO	97	28.2	3.6	28	21	38	0.248	36.0	4.2	36	27	56	0.249	28.9	5.0	28.5	16.4	44.6	0.569
	YES	57	28.8	2.9	28	21	35		36.3	3.0	37	28	42		29.2	3.9	28.4	21.7	37.9	
Beta-blocker	NO	132	28.5	3.4	28	21	38	0.333	36.2	3.8	36	27	56	0.996	29.1	4.6	28.5	19.0	44.6	0.940
	YES	22	27.8	3.4	28	22	34		36.0	3.5	36.5	30	44		28.8	4.8	29.3	16.4	37.2	
Calcium canal blocker	NO	130	28.4	3.4	28	21	38	0.660	36.0	3.8	36	27	56	0.157	29.0	4.8	28.5	16.4	44.6	0.606
	YES	24	28.6	3.2	28	21	34		36.8	3.6	37	28	44		29.3	3.8	28.5	21.7	37.2	
Anticoagula n	NO	148	28.5	3.4	28	21	38	0.636	36.1	3.8	36	27	56	0.136	29.0	4.6	28.5	16.4	44.6	0.787
	YES	6	27.8	2.6	27	25	31		38.0	2.4	38	35	41		29.4	4.9	30.5	23.6	34.2	
ASA	NO	134	28.4	3.4	28	21	38	0.535	36.2	3,9	36	27	56	0.535	29.0	4.7	28.4	19.0	44,6	0,727
	YES	20	28.8	3.5	28.5	22	34		35.5	3,1	36	30	41		28.9	4.3	30.1	16.4	33,9	
Alpha blocker	NO	150	28.4	3.4	28	21	38	0.955	36.1	3.8	36	27	56	0.479	29.0	4.7	28.5	16.4	44,6	0,633
	YES	4	28.3	1.7	28.5	26	30		37.3	1.9	36.5	36	40		28.1	2.7	27.2	25.9	31,9	
Metformin	NO	98	28.1	3.2	28	21	35	0.163	36.0	3.4	36	27	43	0.763	28.4	4.4	28.1	16.4	40,4	**0,026**
	YES	56	29.0	3.6	28.5	22	38		36.3	4.4	36	28	56		30.2	4.8	29.7	19.0	44,6	
DPP4	NO	128	28,3	3.4	28	21	38	0.381	36.2	3.9	36	27	56	0.369	28.8	4.7	28.5	16.4	44,6	0,246
	YES	26	28.9	3.2	28.5	23	34		35.7	3.3	36	30	44		29.9	4.3	29.1	23.0	39.3	
SGLT2	NO	145	28.3	3.3	28	21	38	0.318	36.0	3.7	36	27	56	**0.038**	28.8	4.5	28.5	16.4	44.6	**0.043**
	YES	9	30.0	4.4	30	24	38		38.4	3.3	38	33	44		326	4.9	31.9	27.9	39.3	
Insulin	NO	137	28.3	3.4	28	21	38	0.287	36.2	3.9	36	27	56	0.728	28.9	4.8	28.5	16.4	44.6	0.242
	YES	17	29.2	2.8	28	24	34		35.9	2.0	36	32	39		29.9	3.1	29.0	24.5	34.2	
Levotiroksi n	NO	141	28.4	3.3	28	21	38	0.369	36.2	3.8	36	27	56	0.645	29.0	4.6	28.5	16.4	44.6	0.966
	YES	13	29.1	3.7	30	21	34		35.8	3.2	36	31	43		29.0	5.0	30.4	19.2	39.3	
SSRI/SNRI	NO	149	28.5	3.3	28	21	38	**0.042**	36.2	3.7	36	27	56	0.122	29.1	4.6	28.6	16.4	44.6	0.127
	YES	5	25.2	3.4	24	21	30		33.8	3.7	33	31	40		25.6	4.0	28.0	19.2	28.8	
PPI	NO	116	28.6	3.3	28	21	38	0.418	36.2	3.9	36	27	56	0.904	29.1	4.7	28.5	16.4	44.6	0.691
	YES	38	28.0	3.6	28	21	38		35.9	3.2	36	30	42		28.7	4.5	28.8	19.0	39.3	
Statin	NO	125	28.4	3.3	28	21	38	0.705	36.2	3.9	36	27	56	0.773	29.0	4.6	28.5	16.4	44.6	0.810

ACE: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin 2 receptor blocker, ASA: American Society of Anesthesiologists, DPP-4: Dipeptidyl peptidase- 4 inhibitor, SGLT2: sodium-glucose co-transporter 2, SSRI: Selective serotonin reuptake inhibitor, SNRI: Serotonin-norepinephrine reuptake inhibitör, PPI: Proton-pump inhibitor

Regarding the measurement of the femur neck, 33.1% (n=51) of participants were of average density, 56.5% (n=87) were osteopenic, and 10.4% (n=16) were osteoporotic. No significant difference was detected between albumin, transferrin, CRP, monocytes, and IL-6 levels of standard, osteopenic, and osteoporotic patients when analyzed separately according to the DEXA scans of the lumbar spine and femoral neck.

DISCUSSION

Seventy-seven point nine percent (n=121) of the patients included in our study had a BMI >25 kg/m^2. Forty-two point two percent (n=66) of them were in the obese category. The presence of such a large number of obese patients, according to BMI, among randomly selected patients in the outpatient clinic indicated that obesity is a considerable problem for our country in the elderly population. When the studies in the literature are reviewed, it is seen that the functional capacity decreases, and there is an increase in issues such as the decrease in muscle mass and malnutrition in the groups with BMI <25 kg/m^2 and BMI >35 kg/m^2 in the geriatric population (11). Just as sarcopenia is a notable public health problem in this age group, obesity is similarly crucial.

A study found a positive and significant correlation between serum IL-6, CRP levels, and BMI. When we investigate other studies on this subject today, obesity is recognized as a chronic inflammatory condition and may increase inflammatory markers such as IL-6, TNF-alpha, and CRP (6-9). In our study, no significant difference was detected between the levels of albumin, transferrin, CRP, monocytes, and IL-6 in obese and non-obese patients, contrary to previous reports. Studies in the literature related to the general population, compared to our senior age group population, may have caused this difference.

Our study found a statistically significant and positive correlation between BMI and CRP levels, a finding that is consistent with previous literature, unlike the non-significant relationship between obesity and CRP levels. Considering previous studies, and as a negative acute phase reactant, transferrin, a negative correlation between BMI and transferrin levels would be expected. However, our study found a significant positive correlation that deviates from this expectation (12,13).

In a study by Jalili et al. (14), ALT, ALP, and gamma-glutamyl transferase (GGT) levels were found to be significantly higher in obese individuals compared to non-obese individuals. In another study, ALT, AST, and GGT levels were significantly higher in obese individuals. Similarly, in our research with the geriatric population, ALT, ALP, and LDH levels were significantly higher in obese individuals compared to non-obese individuals (15). It is postulated that the observed increase in liver function tests in obese individuals, as compared to non-obese individuals, may be attributed to obesity being a significant constituent of metabolic syndrome, which is known to contribute to the development of hepatosteatosis. Moreover, consistent with the findings of previous research, our study revealed a statistically significant elevation in lymphocyte counts among obese individuals when compared to their non-obese counterparts (16).

According to studies in the literature, LDL and triglyceride levels are significantly increased in obese patients compared to non-obese patients, whereas HDL levels show no significant difference (17). Similar to the literature, no significant difference was observed in HDL levels in our study. However, unlike the literature, there was no significant difference in LDL and triglyceride levels, which may be attributed to approximately 18% (n=29) of the patients in our study using lipid-lowering drugs in the statin group, potentially affecting the results.

IL-6 is an essential cytokine in the development of inflammatory responses. Previous literature has shown a negative relationship between IL-6 and albumin, a negative acute phase reactant. Similarly, our study found a negative significant relationship between IL-6 levels and albumin levels, suggesting that an increase in IL-6 levels may contribute to malnutrition in the geriatric population by reducing albumin levels. Our study also found a positive, significant relationship between IL-6 and CRP levels and a negative, significant relationship between CRP levels and albumin levels. This suggests that IL-6 is an critical positive acute phase reactant that can cause an increase in CRP levels and a decrease in negative acute phase reactants such as albumin. Monocytes are cells that increase during inflammation and infection. Our study found a significant positive relationship between monocyte levels and both IL-6 and CRP levels, consistent with previous literature.

Previous studies have shown that the use of SSRI/SNRI drugs can lead to weight gain. Similarly, our study found that patients using SSRI/SNRI drugs had a significantly higher arm circumference than those who did not use these drugs. This suggests that SSRI/SNRI drugs may contribute to weight gain in the geriatric population, particularly in obese individuals, and should be used with caution.

Patients using SGLT2 drugs had significantly lower calf circumferences than those who did not use these drugs. Additionally, patients using SGLT2 and metformin had a

significantly lower BMI than those who did not use these drugs. This could be due to metformin's insulin resistance-reducing effect and the weight loss caused by SGLT2 drugs. Similar to our study, previous literature has shown a negative significant relationship between metformin, SGLT2 inhibitors, and BMI.

According to studies in the literature, there is a significant increase in LDL and triglyceride levels in obese patients when compared to non-obese patients, but no significant difference in HDL levels. In our study, similar to the literature, no significant difference was observed in HDL levels. However, unlike the literature, there was no significant difference in LDL and triglyceride levels, which may be attributed to the fact that approximately 18% (n=29) of the patients in our study were using lipid-lowering drugs in the statin group, which could have affected the results.

Our study found a significant positive relationship between arm circumference and calf circumference; calf circumference and BMI; and arm circumference and BMI. This finding is similar to the studies in the literature and suggests that the measurement of arm and calf circumference can be an essential alternative to the BMI (18,19).

IL-6 is an essential cytokine in the development of the inflammatory response. According to the literature, a negative relationship exists between albumin, a negative acute-phase reactant, and IL-6 (20). Similarly, our study found a significant negative correlation between IL-6 levels and albumin levels. Based on these findings, an increase in IL-6 levels may contribute to malnutrition in the geriatric population by reducing albumin levels.

Our study found a significant positive correlation between IL-6 and CRP levels and a significant negative correlation between CRP and albumin levels. This highlights the crucial role of IL-6 as a significant positive acute-phase marker that can reduce negative acute-phase reactants such as albumin while also contributing to increased CRP levels. Monocytes, which are cells that increase during inflammation and infection, were also found to have a significant positive correlation with IL-6 and CRP levels, reflecting their role as inflammatory markers. These findings are consistent with previous studies in the literature (21,22).

The use of SSRI/SNRI drugs has been shown to cause weight gain in a study conducted by Gafoor et al. (23) Consistent with these data, our study found a significant increase in the mean arm circumference of patients taking SSRI/SNRI drugs compared to those who did not use these drugs. This suggests that SSRI/SNRI drugs may lead to weight gain in the geriatric population and should be used with caution, particularly in obese geriatric patients (23).

In individuals using SGLT2 inhibitors, the average calf circumference was significantly lower than those who did not use these medications. The group of patients using SGLT2 inhibitors and metformin had a significantly lower BMI than those who did not. It is believed that the insulin-sensitizing effect of metformin and the weight loss effect of SGLT2 inhibitors contribute to this result. Similar to these findings, the literature shows a significant negative correlation between metformin/SGLT2 inhibitors and BMI (24,25).

In our study, which involved femoral neck and lumbar L1-L4 vertebrae bone density measurements using DEXA in a geriatric population, no significant differences were found between albumin, transferrin, CRP, monocyte, and IL-6 levels in normal, osteopenic, and osteoporotic groups. However, the literature suggests a significant relationship between increased IL-6 levels and osteoporosis, which was not observed in our study, potentially due to limitations such as the inclusion of only geriatric individuals, and a relatively small sample size compared to previous studies (26,27).

CONCLUSION

Our study data revealed that obesity is a significant public health concern, which can trigger various inflammatory processes and increase inflammatory markers. While the direct relationship between IL-6 and obesity remains unclear, our study suggests that IL-6 plays a role in many indirect inflammatory processes triggered by obesity. However, our limited sample size, multiple comorbidities in the geriatric population, and the use of various medications that could limit study data have made it challenging to obtain more precise and significant results.

Further studies are required to elucidate the relationship between IL-6 and laboratory parameters, obesity, and osteoporosis.

ETHICS

Ethics Committee Approval: The study was approved by the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital for Clinical Research (decision number: 2022-10-15, date: 23.05.2022).

Informed Consent: Written informed consent was obtained from all participants before they participated in the study, and their rights and welfare were protected throughout the study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: D.Y., N.I., Consept: E.Ş., N.I., Design: D.Y., E.E., N.I., F.K., Data Collection or Processing:

E.Ş., E.E., F.K., Analysis or Interpretation: E.E., F.K., F.A., Literature Search: E.Ş., F.A., Writing: D.Y., F.A.

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

Financial Disclosure: The authors declare that this study was financially supported by the hospital budget, as approved by the expert board (TUEK) under the decision documented as Ao E-14679818-771.

Acknowledgment

I want to express my thanks to Associate Professor B.E., who provided valuable support in organizing and supervising the study.

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):181-184
DOI: 10.4274/BMJ.galenos.2024.2024-9-2

Research

The Effect and the Histopathological Changes of *Helicobacter Pylori* Infection on the Duodenal Mucosa Among Dyspeptic Patients

Dispeptik Hastalarda *Helicobacter Pylori* Enfeksiyonunun Duodenum Mukozası Üzerindeki Etkisi ve Histopatolojik Değişiklikleri

Mohammed N. Hilmi[1], Batool Mutar Mahdi[2], Jameelah Ghadhban Oudah[3], Wafaa Hazim[3]

[1]Al-Kindy College of Medicine, Department of Pathology and Forensic Medicine, Baghdad, Iraq

[2]Head of HLA Research Unit, Al-Kindy College of Medicine, Department of Microbiology, Baghdad, Iraq

[3]University of Baghdad, Al-Kindy College of Medicine, Department of microbiology, Baghdad, Iraq

ABSTRACT

Objective: *Helicobacter pylori* (*H. pylori*) infection is the main cause of dyspepsia, as it leads to duodenitis and subsequently duodenal ulcers. Early diagnosis of these bacteria by an invasive gastroscopic method combined with a histopathological study is important for eradication of these bacteria to prevent further consequences.

Aim of the study to explore the prevalence of *H. pylori* infection and duodenal histological changes in dyspeptic patients.

Methods: This cross-sectional study consisted of 125 patients who complained of dyspepsia and underwent endoscopy with biopsy taken at Al-Kindy Teaching Hospital in Baghdad, Iraq January 2015 to January 2023.

Results: The age of the patients ranged from 16-70 years (33.16±12.39). Among all dyspeptic patients, 75 (60%) were males and 50 (40%) were females. The histological results showed that the overall prevalence of *H. pylori* was 16% (20 cases) of all cases of duodenitis, and the rest, 84% (105 cases), were negative. Histopathological examination of duodenal mucosa showed a significant increase in villous broadening and shortening by 49.52% in duodenitis without *H. pylori* infection, while in duodenitis with *H. pylori* infection, it was 25% p=0.043.

Conclusion: These results showed a lower prevalence of *H. pylori* among dyspeptic patients with duodenitis, along with a significant histopathologic feature regarding duodenal villi.

Keywords: *Helicobacter pylori*, duodenitis, histopathology

ÖZ

Amaç: *Helicobacter pylori* (*H. pylori*) enfeksiyonu, daha sonra duodenit ve duodenum ülserlerine bağlı dispepsinin başlıca nedenidir. Bu bakterilerin invaziv gastroskop yöntemi ile histopatoloji çalışmasıyla erken teşhisi, bu bakterilerin daha fazla sonuç doğurmasını önlemek için erken eradikasyonu açısından önemlidir.

Dispeptik hastalarda *H. pylori* enfeksiyonunun ve duodenum histolojik değişikliklerinin yaygınlığını araştırmak.

Gereç ve Yöntem: Bu kesitsel çalışma, Ocak 2015 ile Ocak 2023 arasında Irak-Bağdat'taki Al-Kindy Eğitim Hastanesi'nde dispepsi şikayetiyle endoskopi yapılan ve biyopsi alınan 125 hastadan oluşuyordu.

Bulgular: Hastaların yaşları 16-70 yıl (33,16±12,39) arasında değişiyordu. Tüm dispeptik hastalar arasında 75 (%60) erkek ve 50 (%40) kadındı. Histolojik sonuçlar, *H. pylori*'nin genel yaygınlığının tüm duodenit vakalarının (20) %16'sı olduğunu ve geri kalanının (105) (%84) negatif olduğunu gösterdi. Duodenum mukozasının histopatolojik incelemesi, *H. pylori* enfeksiyonu olmayan duodenitlerde villöz genişleme ve kısalmada önemli bir artış (%49,52) gösterirken, *H. pylori* enfeksiyonu olan duodenitlerde bu artış (%25) idi (p=0,043).

Sonuç: Bu sonuçlar, duodenitli dispeptik hastalarda *H. pylori*'nin daha düşük yaygınlığını ve duodenum villusları ile ilgili önemli bir histopatolojik özelliği gösterdi.

Anahtar Kelimeler: *Helicobacter pylori*, duodenit, histopatoloji

Address for Correspondence: Batool Mutar Mahdi, Head of HLA Research Unit, Al-Kindy College of Medicine, Department of Microbiology, Baghdad, Iraq

E-mail: batoolmutar@kmc.uobaghdad.edu.iq **ORCID ID:** orcid.org/0000-0001-6637-8936

Cite as: Hilmi MN, Mahdi BM, Oudah JG, Hazim W. The Effect and the histopathological changes of *Helicobacter Pylori* infection on the duodenal mucosa among dyspeptic patients. Med J Bakirkoy. 2025;21(2):181-184

Received: 15.09.2024
Accepted: 11.01.2025
Publication Date: 04.06.2025

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INTRODUCTION

Dyspepsia is a term originating from two Greek words: the first is "Dus", meaning bad, and the second is "Peptien", which indicates digestion of the upper gastrointestinal tract (1). Globally, 10-37.9% of the population complain of dyspepsia depending on the geographical area (2). In Iraq, it affects about 26-41% of the population (3). The main cause of dyspepsia is pathologies of the upper gastrointestinal tract, such as gastric ulcers, duodenal ulcers, esophagitis, and tumors of the digestive tract (4). Other causes include and bacterial growth of gastrointestinal tract like *Helicobacter pylori (H. pylori)* infection which is the most common bacterial infection of the stomach and duodenum (5,6). Duodenum is the first part of small intestine that receives partially digested food from the stomach and more liable to be colonized with *H. pylori* in the duodenal bulb causing duodenitis and kissing ulcers especially in patients who had unusual anatomy of the bulb (7,8). The main mechanism of this disease is the hypersecretion of acid and gastrin, which leads to the development of gastric metaplasia in the proximal part of the duodenum, which is colonized by *H. pylori*, and a decrease in the secretion of bicarbonate (9). This infection will stimulate the immune system, causing infiltration of neutrophils, resulting in mucosal tissue damage due to the release of proteolytic enzymes and initiation of reactive oxygen metabolites in the duodenal epithelial cells (10). Other inflammatory cells will infiltrate the mucosal tissue are lymphocytes especially in patients infected with cytotoxin-associated gene A positive H. pylori in the bulb of the duodenum with expression of toll-like receptor-2 (TLR) and TLR 10 genes in the histopathological tissues in gastroduodenal disorders with *H. pylori* infection (11). There is also villous obliteration and intraepithelial lymphocytosis with interleukin 37 and the chemokine C-X-C motif chemokine ligand 9 secretions which is the common histopathological features of *H. pylori* infection causing duodenitis (12).

This study will explore the prevalence of *H. pylori* infection and duodenal histopathology in dyspeptic patients.

METHODS

This cross-sectional retrospective study consisted of 125 patients who complained from dyspepsia according to the Rome III criteria (presence of early satiation, postprandial fullness, epigastric pain or burning, in the absence of an organic, systemic or metabolic disease) that referred from their physicians for endoscopy at Al-Kindy Teaching Hosppital-Gastroscope Unitfrom January 2015 to January 2023. The study was approved by the Ethical and Scientific Committee of Al-Kindy College of Medicine and the Ethical and Scientific Committee of Scientific Unit Medical Ethics Committee (decision number: 8, date:14.12.2023). The informed consent was not applicable. The inclusion criteria were patients aged more than15 years of age who complained from dyspepsia and upper abdominal pain while the exclusion criteria were subjects who had evidence or history of gastroduodenal malignancies, duodenal ulcer, gastric ulcer, hepatobiliary or pancreatic diseases, history of drugs intake like immunosuppressive therapy, proton pump inhibitors, antibiotics, non-steroidal anti-inflammatory drugs, pregnancy, hepatic or renal failure. Demographic data, including age and gender, were collected from the patients. All patients were fasting for liquids and foods and exposed to local anesthesia (about 6-9 puffs of 10% Lidocaine spray in their oropharynx) then endoscopy was performed using a flexible gastroscope GIF-H260; Olympus, Tokyo, Japan and display screen; Olympus optical endoscopic visualization-261H liquid crystal display monitor; Olympus, Tokyo, Japan. Four duodenal biopsies were taken from the bulb of the duodenum and others from the antrum and the corpus of the stomach for the detection of *H. pylori* and histopathological examination.

Histopathological analysis: Biopsies were fixed in 10% formalin, then embedded in paraffin blocks and cut in consecutive 3 µm sections. Slides were stained with Hematoxylin and eosin stain and modified Giemsa stain, then were examined blindly by a pathologist.

Statistical Analysis

Data were evaluated using software Statistical Package for the Social Sciences (SPSS) version 26. Descriptive statistics such as frequencies and percentages were calculated. Unpaired Student's t-test was used for comparing the mean values of two groups. The independent-sample chi-square test was used to analyze related categorical variables. A p-value equal to or less than 0.05 was considered statistically significant.

RESULTS

The age of the patients ranged from 16-70 years (33.16±12.39) years. Among all dyspeptic patients, 75 (60%) were males and 50 (40%) were females. The histological results, showed that the overall prevalence of *H. pylori* was 16% (20) of all cases of duodenitis, and the rest, 84% (105), were negative (Figure 1). Macroscopically, the biopsies were tiny, consisting of about two to three soft gray-whitish pieces, each one about 0.2-0.8 cm. Histopathological examination of duodenal mucosa (Figure 2) showed a significant increase in villous broadening and shortening

(49.52%) in duodenitis without *H. pylori* infection, while in duodenitis with *H. pylori* infection the percentage was 25% (p=0.043). Other histologic features like lymphoplasmacytic cells infiltrating the lamina propria, neutrophil infiltration, increased intra-epithelial lymphocytes, crypt hyperplasia, atypical lymphocytes, and gastric metaplasia demonstrated no significant differences between presence or absence of *H. pylori* infection (Table 1).

DISCUSSION

Duodenitis is an inflammation in the duodenal mucosal lining that occurs either alone or with gastritis. In this study, *H. pylori* constitutes about 16% of the causative agent of duodenitis, while another study showed that 90.5% were *H. pylori* positive (13). There is an association between the density of *H. pylori* infection, the inflammatory response, and neutrophil infiltration of the mucosa (14). In the United Kingdom, *H. pylori* was common with increasing age, causing gastritis and duodenitis, which is the opposite of the results of this study, which showed it to be common in the younger age group (33.16±12.39) (15). This may be due to the sample size, differences in the clinical presentation of the patients, environmental factors, dietary habits, smoking, alcohol consumption, and history of other diseases. Another study illustrated that *H. pylori* prevalence was 82.6% in dyspeptic patients and proximal duodenitis was 37.7%, while distal duodenitis was 16.9% (16). Eradication of *H. pylori* in dyspeptic patients with microscopic duodenitis leads to more improvement in their symptoms to a greater extent than in those without microscopic changes of duodenitis (17). Mild inflammation of mucosa of the duodenum is very common in asymptomatic cases, and infiltration with polymorphonuclear cells like neutrophils indicates the activity of the inflammatory process in symptomatic patients, that may progress to duodenal ulcer (18). Even children who are positive for *H. pylori* have symptomatic dyspepsia (19). Thus, duodenal biopsy is very important in diagnosis or monitoring many diseases (20). The gastric metaplasia in this study was 9.52% with *H. pylori* infection, while another study showed that the amount of *H. pylori* in the duodenal bulb was associated with the pathogenesis of duodenal ulcer and the extent of gastric metaplasia in the duodenal bulb (21). Moreover, gastric metaplasia in the duodenum was 87.7% in patients with non-complicated duodenal ulcer and 9.8% in patients with complicated duodenal ulcer, with a sensitivity of 83.6%, specificity at 92.8%, predictive accuracy value of 88.7%, relative risk of the predicted outcome at 7.5, relative risk of a different outcome at 0.11, odds ratio at

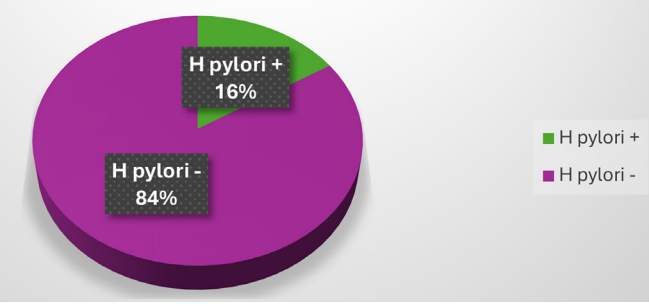


Figure 1. Prevalence of H pylori in duodenitis patients

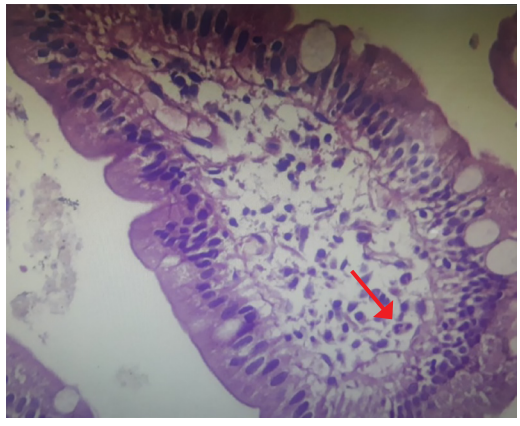


Figure 2. Duodenal villous with Neutrophils infiltration in the core (Arrow). (H&E stain , 40×HPF)

Table 1. Histopathologic features of duodenitis in dyspeptic patients regarding *H. pylori*

Histological Features	*H. pylori* negative No.=105 No.%		*H. pylori* positive No.=20 No. %		p-value
Lymphoplasmacytic cells infiltrating of lamina propria	104	99.04	19	95	0.186
Villous broadening and shortening of mild degree	52	49.52	5	25	*0.043
Increase intra-epithelial lymphocytes	80	64	18	90	0.169
Crypts hyperplasia	40	38.09	6	30	0.491
Atypical lymphocytes.	4	3.80	0	0	NA
Gastric metaplasia	10	9.52	0	0	NA

*Significant, NA: Not applicable

65.4. As a result, the predictive value of gastric metaplasia in the duodenum may be used as a marker of the non-complicated clinical course of duodenal ulcer in *H. pylori* patients (22).

CONCLUSION

These results showed a lower prevalence of *H. pylori* among dyspeptic patients with duodenitis, along with a significant histopathologic feature regarding duodenal villi.

ETHICS

Ethics Committee Approval: The study was approved by the Scientific Unit Medical Ethics Committee of Al-Kindy College of Medicine (decision no: 8, date: 14.12.2023).

Informed Consent: The informed consent was not applicable.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: M.N., B.M.M., J.A., Consept: M.N., B.M.M., J.A., Design: M.N., B.M.M., J.A., Data Collection or Processing M.N., B.M.M., J.A., Analysis or Interpretation: M.N., B.M.M., J.A., Literature Search: M.N., B.M.M., J.A., Writing: M.N., B.M.M., J.A.

Conflict of Interest: The author reports no conflicts of interest in this work

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):185-191
DOI: 10.4274/BMJ.galenos.2024.2024.2-2

Research

What Changes the Sequence of Procedures in Synchronous Upper and Lower Gastrointestinal Endoscopy?

Senkronize Üst ve Alt Gastrointestinal Endoskopide İşlem Sırası Ne Değiştirir?

Yunushan Furkan Aydoğdu[1], Mustafa Örmeci[1], Ali Haldun Özcan[1], Yeşim Akdeniz[2], Alpaslan Fedayi Çalta[2], Serhat Oğuz[2]

[1]Bandırma Training and Research Hospital, Clinic of General Surgery, Balıkesir, Türkiye

[2]Bandırma Onyedi Eylül University Faculty of Medicine, Department of General Surgery, Balıkesir, Türkiye

ABSTRACT

Objective: Bidirectional endoscopy (BDE) refers to esophagogastroduodenoscopy (EGD) and colonoscopy were performed consecutively on the same day. With the widespread use of cancer screening, the question arises of whether EGD or colonoscopy should be performed first. We sought to determine whether EGD or colonoscopy should be performed first in patients undergoing BDE.

Methods: Between February 10 and September 10, 2023, patients who underwent BDE were randomly divided into two groups. Demographic data, EGD duration, colonoscopy duration, transition time, total procedure time, need for additional anesthesia dose, complication status, and patient and endoscopist satisfaction were recorded. Data of a total of 291 patients were evaluated.

Results: A total of 103 patients in the EGD group (group I) and 95 patients in the colonoscopy group (group II) were included in the study. One hundred and seven (54.0%) of the patients were female. The median age of the patients was 59 (18-84) years. The median EGD time was 3 (2-11) min. Inter-procedural transit times were also evaluated. The median duration was 3 (1-6) minutes in group I and 3 (1-8) minutes in group II (p=0.044). The satisfaction of the endoscopists was also questioned. Endoscopist satisfaction was 8.66±1.00 in Group I and 8.12±1.31 in group II (p=0.001). Patient satisfaction was 9.04±0.85 in group I and 8.84±1.29 in group II (p=0.183).

Conclusion: Both procedures are applicable primarily to BDEs. Our study showed that they were not significantly superior to each other. Endoscopist preference will continue to be at the forefront of procedure selection.

Keywords: Bidirectional endoscopy, esophagogastroduodenoscopy, colonoscopy, endoscopist satisfaction, patient satisfaction

ÖZ

Amaç: Çift yönlü endoskopi (BDE), aynı gün içinde ardışık olarak yapılan özofagogastroduedonoskopi (EGD) ve kolonoskopiyi ifade eder. Kanser taramasının yaygınlaşmasıyla birlikte, EGD'nin mi yoksa kolonoskopinin mi önce yapılması gerektiği sorusu ortaya çıkmaktadır. BDE işlemi uygulanan hastalarda önce EGD mi yoksa kolonoskopi mi yapılmalıdır sorusuna yanıt aradık.

Gereç ve Yöntem: 10 Şubat-10 Eylül 2023 tarihleri arasında BDE uygulanan hastalar rastgele iki gruba ayrıldı. Demografik veriler, EGD süresi, kolonoskopi süresi, geçiş süresi, toplam işlem süresi, ek doz anestezi ihtiyacı, komplikasyon durumu, hasta ve endoskopist memnuniyeti kaydedildi. Toplam 291 hastanın verileri değerlendirildi.

Bulgular: İlk işlem olarak EGD uygulanan grupta (grup I) toplam 103 hasta ve kolonoskopi uygulanan grupta (grup II) toplam 95 hasta çalışmaya dahil edildi. Hastaların 107'si (%54,0) kadındı. Hastaların ortanca yaşı 59 (18-84) yıldı. Popülasyondaki ortanca EGD süresi 3 (2-11) dakika idi. Prosedürler arası geçiş süreleri değerlendirildi. Grup I'de ortanca 3 (1-6) dakika, grup II'de ise 3 (1-8) dakika idi (p=0,044). Endoskopistlerimizin memnuniyeti sorgulandı. Endoskopist memnuniyeti grup I'de 8,66±1,00 iken grup II'de 8,12±1,31 idi (p=0,001). Hasta memnuniyeti Grup I'de 9,04±0,85 ve grup II'de 8,84±1,29 idi (p=0,183).

Sonuç: Her iki prosedür de BDE'lerde öncelikli olarak uygulanabilir. Çalışmamız birbirlerine anlamlı üstünlükleri olmadığını göstermiştir. İşlem önceliği seçiminde endoskopist tercihi ön planda olmaya devam edecektir.

Anahtar Kelimeler: Çift yönlü endoskopi, özofagogastroduedonoskopi, kolonoskopi, endoskopist memnuniyeti, hasta memnuniyeti

Address for Correspondence: Yunushan Furkan Aydoğdu MD, Bandırma Training and Research Hospital, Clinic of General Surgery, Balıkesir, Türkiye
E-mail: yfaydogdu92@gmail.com **ORCID ID:** orcid.org/0000-0002-2418-2393

Cite as: Aydoğdu YF, Örmeci M, Özcan AH, Akdeniz Y, Çalta AF, Oğuz S. Detailed examination of bidirectional endoscopy. Med J Bakirkoy. 2025;21(2):185-191

Received: 04.02.2024
Accepted: 31.10.2024
Publication Date: 04.06.2025

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INTRODUCTION

Gastric and colorectal cancers rank among the top five most prevalent types of cancer worldwide (1,2). Gastrointestinal endoscopy is a common screening method for screenings worldwide (3). Gastrointestinal tract cancers are detected at an early stage in Japan and Korea based on advanced screening programs (4). However, the incidence of survival is high (4,5). Bidirectional endoscopy (BDE) involves consecutive esophagogastroduodenoscopy (EGD) and colonoscopy on the same day. BDE is mainly used to investigate positive fecal occult blood tests, iron deficiency anemia, and the cause of bleeding (6). When the literature was reviewed, there was no consensus among the endoscopists who performed the procedure about which procedure should be performed first in BDE (7-10). To contribute to the literature, we evaluated the variability in the procedure order in BDEs performed in our endoscopic procedure unit.

METHODS

Prospectively recorded data related to the study were retrospectively evaluated between February 10 and September 10, 2023. The current study aimed to investigate the optimal sequence for EGD or colonoscopy among patients undergoing BDE. At our tertiary care medical center's endoscopic unit, patients scheduled for BDE for screening were randomly assigned to undergo either EGD or colonoscopy first using a closed envelope method. Subsequently, the patients were divided into two groups and evaluated. Age, gender, body mass index (BMI), blood pressure, saturation, pulse rate, American Society of Anesthesiologists (ASAs) score, gagging during the procedure, EGD time (minutes), colonoscopy time (minutes), transition time between both procedures (minutes), total procedure time (time from anesthesia induction to the end of the procedures, minutes), ileocecal intubation, need for additional dose of anesthesia, and complication status were recorded. The satisfaction of both the endoscopist and patient was evaluated and documented after the procedure [visual analog scale score (1: Very bad, 10: Very good)]. Emergency endoscopic procedures (active bleeding, obstruction), colonoscopic polypectomy or colonoscopic lesion biopsy during the procedure, inadequate bowel preparation, and inaccessible cecum were excluded from the study. A week after surgery, patients were interviewed regarding the possibility of pulmonary infection. The relevant data were then analyzed retrospectively. The endoscopic procedures were performed by five endoscopists at our facility. All endoscopists had at least 5 years of experience in their field. Our endoscopy unit is open five days a week. The unit actively performs procedures approximately 08-16 hours. Endoscopists with 5 years of experience used single-channel endoscopes (EPX-3500 HD, Fujifilm, Singapore; EPK-i5000, Pentax, Japan) for endoscopic procedures. All patients were fasted for 12 hours before the procedure. For oropharyngeal anesthesia, 10% lidocaine spray (IMS Limited, So. El Monte, USA). All patients received midazolam intravenous (i.v.) (2-5 mg) (CURAMED Pharma, Karlsruhe, Germany) and i.v. propofol (1 mg/kg) i.v. (Fresenius Kabi, Hafnerstrasse, Austria) for induction before the procedure. In cases of clinical necessity and need, propofol 0.5 mg/kg was administered additionally. Biopsy was performed during all EGD procedures. The endoscope and colonoscope were cleaned using separate devices before the procedure. The device disinfection and drying process were also applied. Protective equipment such as gloves, aprons, etc.

Were changed during procedure transitions. To prevent bacterial transmission, the procedure area was cleaned, and the drapes used during the procedure were changed. The data of 291 patients were retrospectively evaluated. We excluded 93 patients who did not meet the inclusion criteria. Patients who first underwent EGD were referred to group I, and patients who first underwent colonoscopy were referred to group II. Group I consisted of 103 patients, and group II consisted of 95 patients (Figure 1). Both groups were compared according to the evaluation criteria.

Ethical Consideration

The Bandırma Onyedi Eylül University Rectorate Health Sciences Non-Interventional Research Ethics Board granted approval for the study on (date: 21/12/2023, decision no: 2023-184). The study was carried out in compliance with the principles outlined in the Declaration of Helsinki.

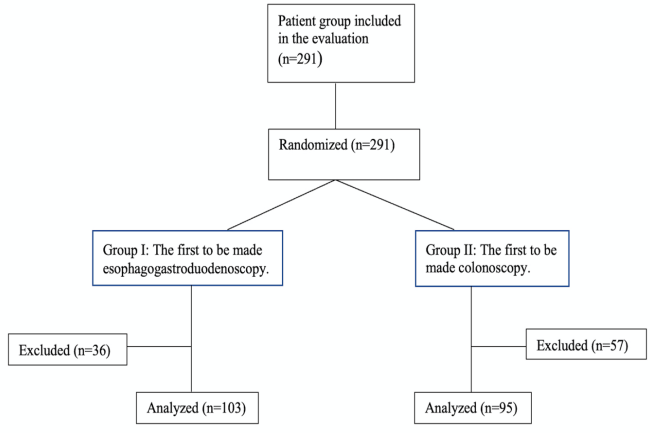


Figure 1. Sample collection scheme

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (version 26.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used, presenting numerical values in the form of median (minimum-maximum) or mean ± standard deviation, while categorical variables were expressed as frequency and percentage. The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test, histogram analysis, and Skewness and Kurtosis data. To examine the uniformity of the numerical parameters across different groups, Levene's test was employed. To compare normally distributed variables between two independent groups, an independent t-test was used, and the Mann-Whitney U test was applied for non-normally distributed parameters. The relationship between binary categorical groups was analyzed using the chi-square test and Fisher's exact test. A significance level of $p<0.05$ was considered.

RESULTS

In this study, 291 patients were randomly included in the BDE plan. Subsequently, 103 patients were included in group I, which first underwent EGD. The exclusion criteria. In the group that underwent colonoscopy first (group II), 95 patients were included. When the entire patient population was detailed according to sex, the female population constituted the majority, with 107 (54.0%) patients. The average age of all patients was 59 years (range, 18-84 years). There were no significant differences in demographic data between the groups. Prior to the procedure, BMI, ASAs scores, systolic and diastolic blood pressure, pulse rate, and saturation were assessed. There were no statistically significant differences in the evaluated data between the groups (Table 1).

The EGD procedure times were evaluated. The median EGD time was 3 (2-11) minutes. In group I, the median EGD time was 4 (2-11) minutes, while in group II, it was 3 (2-8) minutes (p=0.173). The median duration of the colonoscopy procedure was 10 minutes (range: 6-18 minutes). The median duration was 10 minutes (range: 6-18) in group I and 10 minutes (range: 6-15) in group II (p=0.428). The transition time from EGD to colonoscopy in group I and that from colonoscopy to EGD in group II were evaluated. The median was calculated as 3 (1-6) minutes in group I and 3 (1-8) minutes in group II (p=0.044). The BDE times were then calculated. When the entire population was analyzed, the median BDE was calculated to be 17 (10-25) minutes. In group I, the median BDE time was 17 minutes (range: 11-25). In group II, the median duration of BDE was 17 minutes (range: 10-24) (p=0.808) (Table 2).

Complications during EGD and colonoscopy were evaluated. Complications developed in 6 patients. 3.03% of the entire population were patients. The groups were evaluated internally. Complications were noted in three patients in group I and one patient in group II (p=0.92). When the complications were detailed, cardiopulmonary complications occurred in 2 patients, dental trauma in 1 patient, lower gastrointestinal perforation in 2 patients and bleeding in 1 patient. No pulmonary infection or upper gastrointestinal perforation were not observed in

Table 1. Demographic data, ASA score before the procedure, and vital signs at the start of the procedure

	Total (n=198)	Group I (n=103)	Group II (n=95)	p-value
Age, median (range),	59 (18-84)	53 (19-84)	52 (18-82)	0.763*
Sex, n (%)				0.923**
Female	107 (54.0%)	56 (54.5%)	51 (53.7%)	
Male	91 (46.0%)	47 (45.6%)	44 (46.3%)	
BMI, mean (range) kg/m^2	26.60 (20.10-40.40)	26.70 (20.10-40.40)	26.40 (20.30-36.60)	0.998*
ASA score, n (%)				0.940**
ASA1	32 (16.2%)	17 (16.5%)	15 (15.8%)	
ASA2	112 (56.6%)	59 (57.3%)	53 (55.8%)	
ASA3	54 (27.3%)	27 (26.2%)	27 (28.4%)	
Systolic blood pressure, median (range), mmHg	126 (82-184)	125 (95-184)	130 (82-178)	0.575*
Diastolic blood pressure, median (range), mmHg	75.50 (40-127)	75 (40-127)	76 (50-118)	0.745*
Pulse, median (range)	86.50 (56-134)	86 (56-134)	87 (62-128)	0.661*
Saturation, median (range)	97 (68-110)	97 (68-110)	97 (87-100)	0.706*

*Mann-Whitney U test, **Chi-square test, n: Number, kg: Kilograms, m^2: Square meter, BMI: Body mass index, ASA: American Society of Anesthesiologists

any patient (Table 3). The contentment of our experienced endoscopists who conducted the procedures was also called into question. The average satisfaction rating of the endoscopists was 8.40±1.19. In group I, the average satisfaction for endoscopists was 8.66±1.00, whereas in group II, it was 8.12±1.31 (p=0.001). When assessing patient satisfaction, the mean score was 9.04±0.85 in group I and 8.84±1.29 in group II (p=0.183) (Table 3, Figure 2).

DISCUSSION

In this study, patients who underwent BDE in the same session were evaluated prospectively. However, the analysis was performed retrospectively. The retrospective analysis reduced the reliability of the study. Two different groups, group I and group II, were randomly assigned to patients who underwent BDE, and the patients were evaluated.



Figure 2. Endoscopist's and patient's satisfaction

Table 2. Processing times and variables during processing

	Total (n=198)	Group I (n=103)	Group II (n=95)	p-value
EGD duration, median (range),	3 (2-11)	4 (2-11)	3 (2-8)	0.173*
Colonoscopy duration, median (range),	10 (6-18)	10 (6-18)	10 (6-15)	0.428*
Prosedure duration, median (range), minute	17 (10-25)	17 (11-25)	17 (10-24)	0.808*
Transition period, median (range), min	3 (1-8)	3 (1-6)	3 (1-8)	**0.044***
Retching, n (%)				
Yes	73 (36.9%)	47 (45.6%)	26 (27.4%)	**0.008****
No	125 (63.1%)	56 (54.4%)	69 (72.6%)	
Ileocecal intubation rate, n (%)				
Yes	182 (91.9%)	95 (92.2%)	87 (91.6%)	0.866**
No	16 (8.1%)	8 (7.8%)	8 (8.4%)	
Additional anesthetic dose, n (%)				
Yes	119 (60.1%)	63 (61.2%)	56 (58.9%)	0.75**
No	79 (39.9%)	40 (38.8%)	39 (41.1%)	

*Mann-Whitney U test, **Chi-square test, EGD: Esophagogastroduodenoscopy, n: Number

Table 3. Esophagogastroduodenoscopy and colonoscopy complications, endoscopist and patient satisfaction

	Total (n=198)	Group I (n=103)	Group II (n=95)	p-value
Complications, n (%)				
Positive	6 (3.03%)	3 (2.91%)	3 (3.15%)	0.92**
Negative	192 (96.96%)	100 (97.08%)	92 (96.84%)	
Cardiopulmonary complications	2	1	1	
Lung infection, n	0	0	0	
Dental trauma, n	1	0	1	
Upper GI perforation (n)	0	0	0	
Lower GI perforation (n)	2	2	0	
Bleeding, n	1	0	1	
Endoscopist's satisfaction, mean±SD	8.40±1.19	8.66±1.00	8.12±1.31	**0.001***
Patient's satisfaction, mean±SD	8.94±1.08	9.04±0.85	8.84±1.29	0.183*

*Student's t-test, **Chi-square test, n: Number, GI: Gastrointestinal, SD: Standard deviation

The absence of differences in demographic data, BMI data, and vital signs obtained before the procedure between the study groups demonstrates the effectiveness of the randomization process. In previous studies, biases related to randomization were observed in studies related to BDE (6,11). BDE is performed routinely in endoscopy units, primarily for screening. BDE can be initiated using EGD or colonoscopy. Although there may be a priority order among the units, there are no prioritized recommendations in the literature. Studies have tended to focus more on changes related to sedation (12). In order to contribute to the literature, we aimed to compare which procedure should be performed first. We compared the procedure times, procedure success, anesthesia needs, patient satisfaction, and endoscopist satisfaction. With lower sedation doses, side effects such as delayed recovery or desaturation can be reduced. Park et al. (13) and Hao et al. (14) presented a related study. There was information in the literature stating the need for lower anesthesia doses when the EGD procedure was first performed in BDE. Choi et al. (6) stated that performing EGD first creates the need for lower-dose sedation. In our study, there was no significant difference in the need for additional dose anesthesia between the groups (p=0.75). In the Group that underwent EGD first, an additional 61.2% dose was needed. In the colonoscopy-first group, 58.9% needed an additional dose. Although there was no statistically significant difference. The need for additional dose was higher in the group that underwent EGD first. Colonoscopy is a more painful procedure for the patient (15,16). We posit that easier patient tolerance when EGD, which is a secondary procedure, is performed with adequate sedation during colonoscopy is effective in such situations. The need for additional doses decreased with the postponement of the less painful procedure. Sayın et al. (10) found no significant difference between gagging and the order of the procedure in their study. When gagging was evaluated, we found that it was more common in group I (p=0.08). We believe that the higher frequency of gagging was associated with EGD selected as the first procedure because of the effect of the endoscopist before the full effect of sedation was started. Although a statistically significant relationship exists, this should be supported by new studies. Gagging may be an endoscopist-dependent condition. Oner et al. (17) compared patients who only underwent colonoscopy, and underwent colonoscopy after EGD. They then compared the duration of colonoscopy between the two groups. After comparing the results, no statistically significant difference was found between groups. In our study, there was no significant difference between group I and group II in terms of colonoscopy time (p=0.428). Although the groups were not the same, we believe that the change in the procedure order did not change the duration of colonoscopy. We also found that the endoscopy time did not change with the procedure priority in our study (p=0.173). We believe that the main factor determining the procedure time is the endoscopist. Hsieh et al. (18) evaluated which procedure should be performed first. The results of their study found that there was no statistically significant change in EGD time. Colonoscopy and ileocecal intubation times with changes in procedure order. Similarly, in our study, there was no significant change in the related durations. However, we found a statistically significant difference in preparation time for procedures (p=0.044). We believe that the longer duration of this period in the group that primarily underwent colonoscopy was due to the fact that the cleaning of the procedure area due to colonoscopy and the change in protective materials of the patient and endoscopist were more. The complication rate of the entire study population was 3.03%. Complications were observed in three patients in group I and three patients in group II. There was no statistical relationship between the groups in terms of complications (p=0.92). When the complications were detailed, cardiopulmonary complications occurred in 2 patients, dental trauma in 1 patient, lower gastrointestinal perforation in 2 patients and bleeding in 1 patient. Pulmonary infection and upper gastrointestinal perforation were not observed in any patient. The literature has focused on anesthesia complications when evaluating changes in complications according to procedure order. Variations in procedure-related complications with procedure priority were not investigated. According to our study results, the complication status did not change according to procedure priority. More detailed multicenter studies with larger patient populations are needed. Patient and endoscopist satisfaction were evaluated according to procedure priority. There was no statistical significance between the two groups in terms of patient satisfaction. Patient satisfaction was significantly higher in the EGD group than in the non-EGD group. There was a statistically significant difference in endoscopist satisfaction between the groups (p=0.001), and higher satisfaction was reported among endoscopists in the EGD group. Sayın et al. (10) found that both endoscopists and patients reported higher satisfaction when colonoscopy was performed as the first procedure. On the other hand, Carter et al. (19) evaluated only patient satisfaction and found no statistically significant difference in patient satisfaction between the groups.

There are studies showing that nosocomial infections increase with colonoscopy (20,21). To prevent infection, it is important to pay attention to the necessary disinfection

and change of protective equipment. In this study, post-procedural complications were evaluated. Pulmonary infection was not observed in either group. We believe that infection can be prevented with adequate disinfection and replacement of protective equipment. There is a need for multicenter studies involving more endoscopists on this subject.

CONCLUSION

The number of BDEs is increasing with the widespread use of cancer screening. The question of whether EGD or colonoscopy should be performed first is thus raised. Although we endoscopists have a procedure priority according to their own thoughts, the literature does not clearly prioritize (in our center, the habit of performing EGD with priority is more prominent due to its ease in patient preparation). According to our study results, there was no apparent superiority between the procedures. The first two procedures can be performed first. Prospective multicenter studies with a high number of endoscopists are needed to provide definitive information.

ETHICS

Ethics Committee Approval: The Bandırma Onyedi Eylül University Rectorate Health Sciences Non-Interventional Research Ethics Board granted approval for the study on (date: 21/12/2023, decision no: 2023-184).

Informed Consent: Since this study was recorded retrospectively, patient consent was not required.

FOOTNOTES

Authorship Contributions

Sugical and Medical Practices: Y.F.A., M.Ö., A.H.Ö., Y.A., A.F.Ç., Concept: Y.F.A., M.Ö., S.O., Design: Y.F.A., M.Ö., S.O., Data Collection or Processing: Y.F.A., A.H.Ö., S.O.,Analysis or Interpretation: Y.F.A., A.H.Ö., Y.A., Literature Search: Y.F.A., M.Ö., A.H.Ö., Y.A., A.F.Ç., S.O., Writing: Y.F.A., M.Ö., A.F.Ç., S.O.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):192-198
DOI: 10.4274/BMJ.galenos.2025.2025.1-18

Research

Intracranial Atherosclerotic Disease: Do New-Generation Stents Have Better Effect Than Medical Therapy?

İntrakranial Aterosklerotik Hastalık: Yeni Nesil Stentler Tıbbi Tedaviden Daha mı Etkili?

Leyla Ramazanoğlu[1], Işıl Aslan Kalyoncu[1], Murat Fatih Pul[1], Murat Velioğlu[2], Osman Melih Topçuoğlu[3]

[1]University of Health Sciences Türkiye, İstanbul Fatih Sultan Mehmet Training and Research Hospital, Clinic of Neurology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, İstanbul Fatih Sultan Mehmet Training and Research Hospital, Clinic of Radiology, İstanbul, Türkiye
[3]Yeditepe University Faculty of Medicine, Department of Radiology, İstanbul, Türkiye

ABSTRACT

Objective: To compare the results of stenting and medical therapy in patients with intracranial atherosclerotic disease (ICAD).
Methods: Twenty patients treated between August 2021 and April 2024 were retrospectively analyzed.
Results: Age, occlusion site, dual antiplatelet therapy and score-ICAD were statistically significant in patients who underwent intracranial stenting.
Conclusion: Due to the innovations in interventional medicine, stenting may be a better option than medical treatment for patients with ICAD.
Keywords: Intracranial atherosclerotic disease, stenting, medical therapy

ÖZ

Amaç: İntrakranial aterosklerotik hastalığı (İKAH) olan hastalarda stentleme ve tıbbi tedavi sonuçlarını karşılaştırmak.
Gereç ve Yöntem: Ağustos 2021 ile Nisan 2024 arasında tedavi edilen yirmi hasta retrospektif olarak analiz edildi.
Bulgular: İntrakranial stentleme uygulanan hastalarda yaş, oklüzyon yeri, ikili antiplatelet tedavi ve score-İKAH istatistiksel olarak anlamlıydı.
Sonuç: Girişimsel tıptaki yenilikler nedeniyle, İKAH'lı hastalar için stentleme tıbbi tedaviden daha iyi bir seçenek olabilir.
Anahtar Kelimeler: İntrakranial aterosklerotik hastalık, stentleme, medikal tedavi

INTRODUCTION

Intracranial atherosclerotic disease (ICAD) is a considerable risk factor for ischemic stroke. The incidence varies among different populations. ICAD is estimated to represent 8%-46% of cases worldwide (1-3).

Treatment modalities show a difference between acute management and secondary prevention (4). Higher risk of failure of recanalization and poor prognosis were observed in patients with ICAD-related large vessel occlusion (LVO) compared to LVO of other causes (5). Rescue therapy is often required after failure of recanalization and may include intra-arterial antiplatelets such as glycoprotein IIb/IIIa inhibitors or intravenous prasugrel, antithrombotic agents, angioplasty, stenting, or a combination of the above (4,6).

Secondary prevention consists of medical therapy, including the most recommended dual anti-platelet therapy (DAPT), risk factor control, i.e., appropriate management of hypertension (HT), diabetes, hyperlipidemia (HL), obesity, smoking, and physical activity, MF, (angioplasty and stenting), and surgical treatments such as encephaloduroarteriosynangiosis (1,4,7).

In the current study, the aim was to compare the results of stenting and medical therapy in patients with ICAD.

Address for Correspondence: Leyla Ramazanoglu MD, University of Health Sciences Türkiye, İstanbul Fatih Sultan Training and Research Hospital, Clinic of Neurology, İstanbul, Türkiye
E-mail: afleylaak@hotmail.com **ORCID ID:** orcid.org/0000-0001-6406-1687

Cite as: Ramazanoğlu L, Kalyoncu IA, Pul MF, Velioğlu M, Topçuoğlu OM. Intracranial atherosclerotic disease: do new-generation stents have better effect than medical therapy? Med J Bakirkoy. 2025;21(2):192-198

Received: 24.01.2025
Accepted: 20.04.2025
Publication Date: 04.06.2025

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METHODS

Participants

We retrospectively reviewed the medical records of all patients with symptomatic ICAD between August 2021 and April 2024. Inclusion criteria were: (1) age >18 years, (2) anterior or posterior circulation intracranial artery stenosis of at least 70%, (3) ischemic stroke or transient ischemic attack (TIA) in the previous 3 months, (4) undergoing stenting or receiving best medical therapy. Patients with non-atherosclerotic stenosis such as vasculitis or dissection, and patients with LVO due to ICAD who underwent acute EVT were excluded. This study University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Scientific Research Ethics Committee (number: B.10.1.TKH.4.34.H.GP.0.01/41, date: 08.02.2024).

Data Collection and Follow-Up Outcomes

For each subject, baseline characteristics (age, sex, co-morbid diseases), onset time, antithrombotic drugs prior to onset, modified Rankin Scale (mRS) score prior to onset, National Institutes of Health Stroke Scale (NIHSS) score at admission, major arterial stenosis site, type of stenting devices, intraprocedural administration of loading antiplatelets, procedural complications, degree of reperfusion, continuation of medications, and CHA_2DS_2-VASc were evaluated. Blood glucose, blood pressure, and lipid profiles at admission were recorded.

Definitions

European Cooperative Acute Stroke Study II criteria were used for defining intracranial hemorrhage. Symptomatic intracerebral hemorrhage was defined as any hemorrhage associated with a worsening of the NIHSS score ³4 within 24 hours. Extracranial complications were defined as pneumonia, urinary tract infections, acute renal failure, hematuria and gastrointestinal bleeding. CHA_2DS_2-VASc is a score, that can help to determine the one-year risk of thromboembolism events in non-anticoagulant patients with non-valvular atrial fibrillation (AF). The other parameters were age, sex, history of congestive heart failure, HT, cerebral and peripheral arterial disease, and diabetes. Follow-up was conducted through telephone interviews or outpatient clinic visits. mRS of ≤2 was considered a good clinical outcomes. At the follow-up day 90, 1 year and 2 years, patients were divided into three groups: good prognosis (mRS ≤2), poor prognosis (2< mRS ≤5) and mortality (mRS=6). Score-ICAD (8) is a 20-point scale: absence of AF (5); vascular risk factor burden (1) for each of HT, diabetes, smoking, and HL, multifocal single artery stenoses on CT angiography (3); absence of territorial cortical infarct (3); presence of borderzone infarct (3), and ipsilateral carotid siphon calcification (2).

Stenting Procedure

The stenting procedure was performed using a standard transfemoral approach, under general anesthesia. A bolus of 70-100 IU/kg of heparin was given intravenously immediately after insertion of the long femoral sheath. A long guiding sheath was placed within the cervical internal carotid artery (ICA) or vertebral artery. A 6-French distal access catheter [Fargo (Balt Extrusion, Montmorency, France), Neuron (Stryker, Fremont, California, USA), or Navien (Covidien, Irvine, California, USA)] was then placed coaxially within the guiding sheath. The stenotic segment was bypassed with a balloon catheter (NeuroSpeed; Acandis GmbH, Pforzheim, Germany). The balloon was inflated slowly at the level of stenosis, and the Credo stent (Acandis GmbH, Pforzheim, Germany) was deployed through the balloon catheter. A critical stenosis in the middle segment of the basilar artery and a stenosis in the M1 segment of the middle cerebral artery (MCA) before and after the stenting procedure are shown in figures 1 and 2.

Prior to the intervention, all the patients were mostly on DAPT with aspirin and ticagrelor. DAPT was continued for at least 6 months, after which it was switched to monotherapy, usually as 100 mg aspirin. Management of other risk factors such as blood pressure, HL, and diabetes was done.

Statistical Analysis

Number (n) and percentage (%) values were used to show the distribution of individuals within demographic categories.

The suitability of the continuous variables in the study for normality was evaluated graphically and with the Shapiro-Wilk test. Mean ± standard deviation and Median (minimum-maximum) values were used to display the descriptive statistics of the variables.

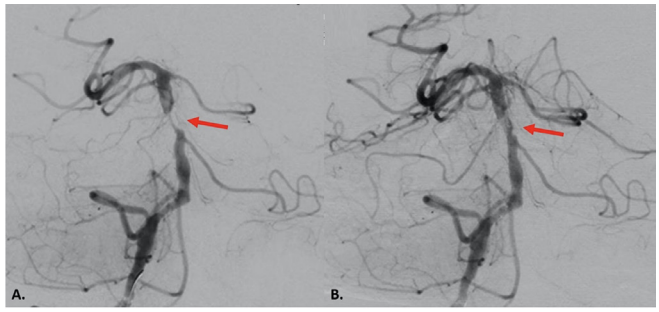


Figure 1. Right vertebral artery injection (A) shows a critical stenosis (arrow) in the middle segment of the basilar artery, in a 79-year-old man with a medical history of recurrent posterior system strokes. After deployment of the Credo (Acandis) and Elvis Evo (MicroVention, Aliso Viejo, CA, USA) stents, the right vertebral artery injection (B) shows restored flow in the stenotic segment (arrow)

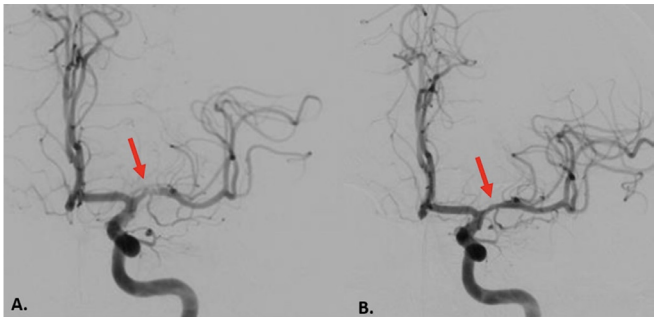


Figure 2. Left internal carotid artery injection (A) shows a stenosis (arrow) in the M1 segment middle segment of the middle cerebral artery, in a 64-year-old woman with a medical history of recurrent left hemispheric strokes. After deployment of the Credo stent (Acandis), the left internal carotid artery injection (B) shows restored flow in the stenotic segment (arrow)

Independent sample t-test, CHA_2DS_2-VASc score, arrival glucose, systolic blood pressure, NIHSS, mRS, 24th hour NIHSS, Mann-Whitney U test was used to compare 90th day mRS, exit treatment time, and triglyceride values.

Cross tables were created to compare categorical variables according to intracranial stent placement status, and number (n), percentage (%), and chi-square (c^2) test statistics were given.

IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 programs were used for statistical analyses and calculations. The statistical significance level was accepted as a $p<0.05$.

RESULTS

A total of 20 patients met the inclusion criteria. The average age of the patients participating in the study was 70.45±8.27 years. Forty percent (n=8) of the patients were female and 60.0% (n=12) were male. HT was present in 19 patients (95.0%), diabetes mellitus in nine (45.0%), HL in eight (40.0%), coronary artery disease in six (30.0%), cerebrovascular disease in six (30.0%), TIA in nine (45.0%). Four patients (20.0%) were found to have AF. At admission, 35.0% (n=7) of the patients had no antiplatelet therapy, 50.0% (n=10) had monotherapy, 10.0% (n=2) had DAPT, and 5.0% (n=1) had anticoagulant and antiplatelet therapy. The average CHA_2DS_2-VASc score of patients was 5.20±1.24. There were three patients with direct oral anticoagulant (15.0%) and four with anti-lipid treatment (40.0%). The mean serum glucose level at admission was 139.95±66.47 mg/dL, the systolic blood pressure average was 161.20±26.15, the diastolic blood pressure average was 86.85±12.17, the mRS average was 0.20±0.52, and the NIHSS average was 1.90±2.57. Thirty-five percent (n=7) of the stenosis site sites were basilar, 55.0% (n=11) were MCA, 5.0% (n=1) were ICA, and 5.0% (n=1) were vertebral. The average post-stroke elective stenting period was 22.93±20.27 days. Additionally, it was found that 10 patients (71.5%) had Credo 4x20, two (14.3%) had Credo 3x20, and one (7.1%) had Credo 4x15 and Credo 5x20. The 24th hour NIHSS was 2.05±2.66. There were two patients (10.0%) with hemorrhagic transformation in the stenting group. The 90th day mRS was 0.80±1.06. While 70.0% (n=14) of the patients had an intracranial stent, 30.0% (n=6) were treated with medical therapy. The discharge treatment of patients was as follows: 45.0% (n=9) received aspirin+ticagrelor, 30.0% (n=6) received aspirin+clopidogrel, 10.0% (n=2) received monotherapy with ticagrelor, 10.0% (n=2) received apixaban+clopidogrel, and 5.0% (n=1) received aspirin+ticagrelor+rivaroxaban. The average treatment time was 8.72±7.13 months. The total cholesterol was 190.20±60.52 mg/dL, the low-density lipoprotein cholesterol, was 120.35±53.22 mg/dL, the high-density lipoprotein cholesterol was 41.95±10.75 mg/dL, the triglycerides were 147.65±77.89 mg/dL, and the ICAD score was 15.00±2.92 (Table 1).

The average age of patients who were treated with medical therapy was 76.50±7.56 years, and the average age of patients who underwent intracranial stenting was 67.86±7.34 years. A statistically significant difference was detected between the ages of patients based on stenting status ($t=2.394$, $p=0.028$). The stenosis site was MCA in all (n=6) patients with medical therapy; basilar was the stenotic site in 50.0% (n=7) of patients who underwent stenting; MCA in 35.8% (n=5); and others (ICA and vertebral) in 14.2% (n=2). A statistically significant difference was detected in terms of site of stenosis in the stenting group ($\chi^2=7.013$, $p=0.038$). The discharge treatment was aspirin+clopidogrel in the medical therapy group (n=6). Aspirin+ticagrelor was given in 64.3% (n=9) of the patients who underwent stenting, and apixaban+clopidogrel was the discharge treatment in 14.3% (n=2). Two patients had mono ticagrelor, and one had aspirin+ticagrelor+rivoraxaban. A statistically significant difference was detected in terms of discharge treatment in the stenting group ($\chi^2=17.642$, $p<0.001$). The average ICAD score was 13.33±2.58 for patients with medical therapy, and 16.67±2.34 for patients with stenting. A statistically significant difference was seen between the ICAD scores of patients ($t=2.334$, $p=0.041$). No statistically significant difference was detected in other parameters ($p>0.05$). No stent restenosis was seen in the study group (Table 2).

Table 1. Demographic characteristics of study group

	All patients (n=20)
Age (year) Avr±SD	70.45±8.27
Gender, n (%)	
Female	8 (40.0)
Male	12 (60.0)
Co-morbidities, n (%)	
HT	19 (95.0)
DM	9 (45.0)
HL	8 (40.0)
PAD	0 (0.0)
CAD	6 (30.0)
CVD	12 (60.0)
TIA	9 (45.0)
CHF	0 (0.0)
AF	4 (20.0)
Admission antiplatelet, n (%)	
Non	7 (35.0)
Mono	10 (50.0)
Dual	2 (10.0)
With Anticoagulant	1 (5.0)
Cha_2ds_2vasc Avr±SD	5.20±1.24
Doac, n (%)	
No	17 (85.0)
Yes	3 (15.0)
Anti-Lipid, n (%)	
No	12 (60.0)
Yes	8 (40.0)
Admission glucose Avr±SD	139.95±66.47
Admission systolic pressure Avr±SD	161.20±26.15
Admission diastolic pressure Avr±SD	86.85±12.17
mRS Avr±SD	0.20±0.52
NIHSS Avr±SD	1.90±2.57
Stenosis site, n (%)	
Basilar	7 (35.0)
MCA	11 (55.0)
ICA	1 (5.0)
Vertebral	1 (5.0)
***Time to stenting** (day) Avr±SD	22.93±20.27
24 hour NIHSS Avr±SD	2.05±2.66
90 Day mRS Avr±SD	0.80±1.06
Intracranial stent, n (%)	
No	6 (30.0)
Yes	14 (70.0)
Discharge treatment, n (%)	
Asa + ticagrelor	9 (45.0)
Asa + ticagrelor + rivoraxaban	1 (5.0)
Apixaban + clopidogrel	2 (10.0)
Mono ticagrelor	2 (1.00)
Asa + clopidogrel	6 (30.0)
Discharge treatment period (month) Avr ± SD	8.72±7.13
Stent re-stenosis, n (%)	
No	20 (100.0)
Total Cholesterol Avr±SD	190.20±60.52
LDL-C Avr±SD	120.35±53.22
HDL-C Avr±SD	41.95±10.75
Triglyceride Avr±SD	147.65±77.89
ICAD score Avr±SD	15.00±2.92

*Only stenting patients
SD: Standard deviation, HT: Hypertension DM: Diabetes mellitus, HL: Hyperlipidemia, PAD: Peripheral artery disease,
CAD: Coronary artery disease, CVD: Cerebrovascular disease,
TIA: Transient ischemic attack, CHF: Congestive heart failure,
AF: Atrial fibrillation, mRS: Modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, MCA: Middle cerebral artery, ICA: Internal carotid artery, Asa:
LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, ICAD: Intracranial atherosclerotic disease

DISCUSSION

Age, stenosis site, DAPT, and score-ICAD were statistically significant in patients who underwent intracranial stenting in this study.

EVT of ICAD is in evolution (1). Stenting vs Aggressive Medical Therapy for Intracranial Artery Stenosis and the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy trials showed worse prognosis in the stenting group than in patients with medical therapy (9,10). As a result, EVT with intracranial angioplasty and/or stenting is not recommended as a first-choice treatment (1,4,5,7). EVT of LVO strokes due to ICAD is also challenging (11,12). In our study, we compared the patients who had symptomatic ICAD and underwent stenting for secondary prevention with patients who had symptomatic ICAD and were treated with medical therapy.

Age is a non-modifiable risk factor for atherosclerosis, and the incidence of ICAD increases with age (13). In our study, there was a statistically significant difference in age between groups. In the stenting group, the population was younger. Serious adverse events were more commonly associated with increased age in patients who underwent intracranial stenting due to ICAD (14). Younger age was associated with new or recurrent infarcts in post hoc analysis of mechanisms of early recurrence in ICAD (15). Adverse events and the risk of recurrent stroke in the young patient population would influence operator choice when deciding on stenting.

Table 2. Comparison of stenting versus medical therapy

	Intracranial stent			
	No (n=6)	**Yes (n=14)**	**Test statistics**	
	Avr±SD Median (Min.-Max.)	**Avr±SD Median (Min.-Max.)**	**t; c^2; z**	**p-value**
Age (year)	76.50±7.56	67.86±7.34	t=2.394	0.028
	76.0 (66-89)	67.0 (56-81)		
Gender, n (%)				
Female	4 (66.7)	4 (28.6)	-	0.137*
Male	2 (33.3)	10 (71.4)		
Comorbidities, n (%)				
HT	5 (83.3)	14 (100.0)	-	0.300*
DM	1 (16.7)	8 (57.1)	-	0.119*
HL	2 (33.3)	6 (42.9)	-	0.545*
CAD	1 (16.7)	5 (35.7)	-	0.387*
CVD	3 (50.0)	9 (64.3)	-	0.455*
TIA	3 (50.0)	6 (42.9)	-	0.574*
AF	1 (16.7)	3 (21.4)	-	0.657*
Admission antiplatelet, n (%)				
No	2 (33.3)	5 (35.7)	=1.569	0.870
Mono	4 (66.7)	6 (42.9)		
Dual	0 (0.0)	2 (14.3)		
With anticoagulant	0 (0.0)	1 (7.1)		
Cha_2ds_2vasc	5.50±0.84	5.07±1.38	z=0.646	0.547
	6.0 (4-6)	5.0 (3-7)		
Doac, n (%)				
No	6 (100.0)	11 (78.6)	-	0.319*
Yes	0 (0.0)	3 (21.4)		
Anti-Lipid				
No	3 (50.0)	6 (64.3)	-	0.455*
Yes	3 (50.0)	5 (35.7)		
Admission glucose	129.00±68.02	144.64±67.81	z=1.279	0.207
	106.0 (85-265)	118.0 (96-343)		
Admission systolic pressure	168.33±24.63	158.14±27.06	z=0.829	0.444
	175.0 (130-200)	150.0 (120-225)		
Admission diastolic pressure	89.33±15.51	85.79±10.95	t=0.587	0.565
	85.0 (70-110)	83.0 (70-110)		
mRS	0.00±0.00	0.29±0.61	z=1.195	0.494
	0.0 (0-0)	0.0 (0-2)		
NIHSS	2.50±3.89	1.64±1.91	z=0.177	0.904
	0.0 (0-8)	1.5 (0-6)		
Stenosis site, n (%)				
Basilar	0 (0.0)	7 (50.0)	=7.013	0.038
MCA	6 (100.0)	5 (35.8)		
Other	0 (0.0)	2 (14.2)		
24 Hour NIHSS	2.17±3.37	2.00±2.45	z=0.353	0.779
	0.0 (0-7)	1.5 (0-8)		

Table 2. Continued

	Intracranial stent			
	No (n=6)	**Yes (n=14)**	**Test statistics**	
	Avr±SD Median (Min.-Max.)	**Avr±SD Median (Min.-Max.)**	**t; c^2; z**	**p-value**
Hemorrhagic transformation, n (%)				
No	6 (100.0)	12 (85.7)	-	0.479*
Yes	0 (0.0)	2 (14.3)		
90 Day mRS	0.17±0.41	1.07±1.14	z=1.945	0.076
	0.0 (0-1)	1.0 (0-3)		
Discharge treatment, n (%)				
Asa+ticagrelor	0 (0.0)	9 (64.3)	=17.642	<0.001
Asa+ticagrelor+rivaroxaban	0 (0.0)	1 (7.1)		
Apixaban+clopidogrel	0 (0.0)	2 (14.3)		
Mono ticagrelor	0 (0.0)	2 (14.3)		
Asa+clopidogrel	6 (100.0)	0 (0.0)		
Treatment time (month)	14.17±10.93	6.00±0.0	z=1.549	0.291
	15.0 (1-24)	6.0 (6-6)		
Total cholesterol	203.83±59.55	184.36±62.18	t=0.649	0.524
	211.5 (104-286)	185.0 (105-337)		
LDL-C	126.50±54.40	117.71±54.56	t=0.330	0.745
	131.0 (38-208)	111.5 (29-231)		
HDL-C	46.67±8.31	39.93±11.29	t=1.309	0.207
	47.0 (34-59)	40.0 (11-56)		
Triglyceride	151.67±60.64	145.93±86.28	z=0.660	0.547
	157.0 (78-247)	126.0 (63-366)		
ICAD score	13.33±2.58	16.67±2.34	t=2.334	0.041
	13.5 (9-17)	17.0 (14-19)		

SD: Standard deviation, Min.: Minimum, Max.: Maximum, HT: Hypertension DM: Diabetes mellitus, HL: Hyperlipidemia, CAD: Coronary artery disease, CVD: Cerebrovascular disease, TIA: Transient ischemic attack, AF: Atrial fibrillation, mRS: Modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, ICAD: Intracranial atherosclerotic disease

In this study, there were seven patients with basilar ICAD, and all underwent stenting. There are studies showing that recurrent stroke/ TIA rates were higher in patients with symptomatic posterior-circulation ICAD (5). Furthermore, basilar artery strokes are one of the most devastating neurological conditions (16). This would explain the tendency for stenting basilar ICAD.

DAPT is recommended for patients with symptomatic ICAD (17). The data is unclear regarding the choice of aspirin and clopidogrel or aspirin and ticagrelor as DAPT following stenting. In our center, due to the risk of clopidogrel resistance, there is a tendency to choose aspirin and ticagrelor treatment, and continue maintenance for six months in patients undergoing intracranial stenting. There was a statistically significant difference in post-stenting therapy. Aspirin and ticagrelor as DAPT were a significant therapy.

A Tarek et al. (8) developed and validated a scoring system for pre-thrombectomy diagnosis of ICAD (8). They showed that scores ≥12 were associated with 90% specificity and 63% sensitivity. In our study, the average ICAD score was 15. The score was higher in the stenting group, and the difference was statistically significant. The Score-ICAD may be useful not only for pre-thrombectomy but also for elective stenting. This Score-ICAD also underlines the vascular risk factors, so patients with excess might be candidates for stenting in our study.

Recent data suggest that delayed stenting, a mean of 21 days or longer, post event may be potentially superior to medical therapy (1). In our study, the average time from symptom onset to stenting was 22 days. No in-stent restenosis was seen in our series.

Study Limitations

There are some limitations in the present study. This was a retrospective study, and the sample size was small. Clopidogrel resistance was not evaluated in all patients. Only the Credo stent was used for the stenting of the lesions.

CONCLUSION

In conclusion, with new-generation stents, stenting may have a greater role in the secondary prevention of ICAD than the best medical treatment. Further studies are needed.

ETHICS

Ethics Committee Approval: This study University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Scientific Research Ethics Committee (decision no: 234344965, date: 08.02.2024).

Informed Consent: Retrospective study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: L.R., I.K.A., M.V., Consept: L.R., Design: LR., Data Collection or Processing: L.R., I.K.A., M.F.P., Analysis or Interpretation: L.R., O.M.T., Literature Search: L.R., M.F.P., Writing: L.R., O.M.T.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):199-206
DOI: 10.4274/BMJ.galenos.2025.2025.1-10

Research

Early Results in Octogenerian Patients Undergoing Endovascular Aortic Aneurysm Repair and its Effect on Karnofsky Scoring: A Single Center, Retrospective Study

Endovasküler Aort Anevrizmasi Onarımı Uygulanan Oktojeneryan Hastalardaki Erken Dönem Sonuçlar ve Karnofsky Skorlamasina Etkisi: Tek Merkezli, Retrospektif Çalışma

Gülsüm Türkyılmaz[1], Mehmet Ali Yeşiltaş[2], Onur Emre Satılmış[1], Hasan Toz[1], Yusuf Kuserli[1], Saygın Türkyılmaz[1], Ali Aycan Kavala[1]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiovascular Surgery, İstanbul, Türkiye

[2]Şişli Kolan Hospital, Clinic of Cardiovascular Surgery, İstanbul, Türkiye

ABSTRACT

Objective: With the increase in life expectancy, the octogenarian population is expected to increase in our country as well as in the whole world. We aimed to examine the periprocedural and early period mortality, morbidity, and functional status of the patients to whom we applied endovascular aortic repair (EVAR) electively.

Methods: The data of all patients aged 80 years and older who applied to our clinic with the diagnosis of abdominal aortic aneurysm (AAA) between January 2014 and December 2023, and who underwent elective EVAR, were analyzed retrospectively. Mortality and morbidity of all patients were evaluated during the periprocedural period and in the early postoperative period. Patients were evaluated according to the Karnofsky performance status scale and their quality of life.

Results: EVAR was applied to 36 patients. The mean age of the octogenarian patient group in our study was 84 (80-91) years. Patients are mostly male (83.3%). The procedure was performed under general anesthesia in all patients. One unit of erythrocyte suspension was used. it was observed that there was no endoleak on the 30th day. The procedure was completed successfully in all patients. There was no mortality in the 30-day follow-up. Improvement was observed with all patients in Karnofsky scoring both on the 2nd postoperative day and on the 30th day.

Conclusion: EVAR, which has equal success with open surgery in patients with AAA in the octogenarian, will significantly reduce operative morbidity, intensive care unit, and hospital stay and cost when performed in an experienced and high-volume center. In addition, we believe that these patients who are octogenarians improve their performance more quickly.

Keywords: Endovascular aortic repair, octogenerian, karnofsky scale, abdominal aortic aneursym

ÖZ

Amaç: Yaşam beklentisindeki artışla birlikte, tüm dünyada olduğu gibi ülkemizde de 80 yaş ve üzeri nüfusun artması beklenmektedir. Elektif olarak endovasküler aort onarımı (EVAR) uyguladığımız hasta grubunda hastaların periprosedürel ve erken dönem mortalite, morbidite ve fonksiyonel durumlarını incelemeyi amaçladık.

Gereç ve Yöntem: Ocak 2014 Aralık 2023 tarihleri arasında kliniğimize abdominal aortic aneurysm (AAA) tanısıyla başvuran ve elektif EVAR uygulanan 80 yaş ve üzeri tüm hastaların verileri retrospektif olarak incelendi. Tüm hastaların mortalite ve morbiditeleri periprosedürel ve erken dönemde değerlendirildi. Hastalar Karnofsky performans durum ölçeğine ve yaşam kalitelerine göre değerlendirildi.

Bulgular: Otuz altı hastaya EVAR uygulandı. Çalışmamızdaki 80 yaş ve üzeri hasta grubunun ortalama yaşı 84 (80-91) idi. Hastalar çoğunlukla erkekti (%83,3). Tüm hastalarda işlem genel anestezi altında yapıldı. Ortalama 1 ünite eritrosit süspansiyonu kullanıldı. Otuzuncu günde endoleak

Address for Correspondence: Gülsüm Türkyılmaz, MD, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiovascular Surgery, İstanbul, Türkiye
E-mail: oztrose@hotmail.com **ORCID ID:** orcid.org/0000-0001-6910-7664

Received: 25.01.2025
Accepted: 11.02.2025
Publication Date: 04.06.2025

Cite as: Türkyılmaz G, Yeşiltaş MA, Satılmış OE, Toz H, Kuserli Y, Türkyılmaz S, et al. Early results in octogenerian patients undergoing endovascular aortic aneurysm repair and its effect on karnofsky scoring: a single center, retrospective study. Med J Bakirkoy. 2025;21(2):199-206

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ÖZ

olmadığı görüldü. İşlem tüm hastalarda başarıyla tamamlandı. Otuz günlük takipte mortalite olmadı. Tüm hastalarda hem postoperatif 2. günde hem de 30. günde Karnofsky skorlamasında iyileşme gözlendi.

Sonuç: Seksen ve üzeri yaştaki AAA'lı hastalarda açık cerrahi ile eşit başarıya sahip olan EVAR, deneyimli ve yüksek hacimli bir merkezde yapıldığında operatif morbiditeyi, yoğun bakım ünitesini ve hastanede kalış süresini ve maliyeti önemli ölçüde azaltacaktır. Ayrıca, 80 ve üzeri yaştaki bu hastaların performanslarını daha hızlı iyileştirdiğine inanıyoruz.

Anahtar Kelimeler: Endovasküler aort onarımı, oktojeneryan, karnofsky skala, abdominal aort anevrizması

INTRODUCTION

Today, with the increase in life expectancy, the octogenarian population is expected to increase in our country as well as in the whole world (1). Abdominal aortic aneurysm (AAA) is a disease that is often asymptomatic, and its frequency increases with age. The annual risk of rupture in untreated AAA increases with vessel diameter. While the risk of 5-cm-and-above AAA rupture is 3-15%, the risk of 8 cm AAA rupture is more than 50%. Therefore, AAA with an aneurysm diameter of 5.5 cm or more should be treated (2,3).

Endovascular abdominal aortic replacement (EVAR) has been widely applied as an alternative to surgical treatment for AAA with the development of technology in endovascular treatments (4,5). The risk of mortality and morbidity is high in open AAA surgery therefore especially in elderly and frail patients the tendency to prefer EVAR is getting more (6). Considering the risk factors brought by EVAR in elderly asymptomatic patients , there is still no consensus on whether to treat the condition or not. We see that mid-term and procedural results are shared with octogenarian and non-agenarian patients at the studies in recent years (7-10).

In this study, we also examined octogenarians in our own clinic. We aimed to examine the periprocedural and early period mortality, morbidity and functional status of the patients to whom we applied EVAR electively in the patient group.

METHODS

This study University of Health Sciences Türkiye, Bakırköy Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2022-17-09, date: 05.09.2022). The data of all patients aged 80 years and older, who applied to our clinic with the diagnosis of AAA between January 2014 and December 2023, and who underwent elective EVAR were analyzed retrospectively. Patients aged 80 years and older were defined as octogenarians. Demographic information, intraoperative data, and postoperative results of the patients were collected through the hospital data processing system and from patient files (Table 1,2).

Coronary artery disease (CAD), hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), kidney disease (chronic kidney failure defined by serum creatinine >1.2 mg/dL in the last 3 measurements), smoking, congestive heart failure, history of cerebrovascular accident (stroke and/or transient ischemic attacks), history of cancer (current malignancy or any past incidence), dyslipidemia, and atrial fibrillation were considered as comorbidities.

EVAR procedures were performed on patients with few comorbidities, high surgical risk, and suitable aortic anatomy. Aneurysm size and anatomical features (aortic neck length and angulation, iliac artery diameter, calcification, and kinking) were determined preoperatively by computed tomography angiography. Patients were evaluated according to the Karnofsky performance status scale, and their quality of life was assessed separately (11,12).

Table 1. Inclusion and Exclusion criteria

Inclusion criteria;	Exclusion criteria;
Anatomically suitable patients for EVAR	Patients not eligible for the EVAR procedure.
High-risk patients for Open Surgery	Anatomically suitable patients.
	Patients with severe hemodynamic instability.
	Patients who cannot undergo CTA.
	Cases those needed open surgery during the EVAR procedure.
	Patients who have had open surgery or EVAR in the past.

EVAR: Endovascular aneurysm repair, CTA: Computed tomography angiography

Table 2. Baseline characteristics of octogenerians undergoing EVAR

		median (min.-max.)	n	%
Age , years		**84 (80-91)**		
Gender				
	Female		30	83.3
	Male		6	16.7
BMI		39.7-18.2) 24.7)		
Comorbidities				
	Smooking		21	58.3
	CHF		6	10
	Hipertension		32	88.9
	Diabetes mellitus		6	16.7
	COPD		5	8.3
	ESRD		8	13.3
	PAD		10	27.8
	CAD		20	55.5
	Prior PCI		14	38.9
	Prior CABG		6	16.7
Preoperative medications				
	Aspirin		22	61.1
	Statin		26	72.2
	ACE-i		32	88.9
	ß-blocker		21	58.3
	Clopidogrel		7	19.4
	Anticoagulation		2	5.5
Asymptomatic			22	61.1
Symptomatic			14	38.9
Laboratory				
	Hemoglobin	12.1 (7.1-15.2)		
	Hematocrit	36.2 (22.3-53.1)		
	Kreatinin	1.05 (0.6-2.4)		
	LDL-cholesterol	100 (30-205)		

Min.-max.: Minimum-maximum, BMI: Body mass index, CHF: Chronic heart failure, COPD: Chronic obstruction pulmonary disease, ESRD: End stage renal disease, PAD: Peripheral artery disease, CAD: Coronary artery disease, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass grafting, ACE-i: Angiotensin-converting-enzyme inhibitors, LDL: Low-density lipoprotein

Interventional Procedure

In endovascular cases, stent graft placement was performed via femoral access (openly prepared or percutaneously) under general anesthesia with Endurant™ II/IIs AAA stent graft system (Medtronic, USA). In case of emergency, endografts of appropriate diameter that can be used immediately are employed.

Outcomes

Primary outcomes are technical success and freedom from mortality in 30 days. Secondary endpoints consisted of surgical graft complications (graft thrombosis, graft infections, hemorrhage, aortoiliac pseudoaneurysms) and EVAR complications (endoleak, aneurysm enlargement, graft migration, AAA rupture, secondary interventions, and need of open surgical procedures). Perioperative complications were defined as myocardial infarction, stroke, visceral organ ischemia, arterial ischemia, renal failure, pulmonary complications, and entry site hematoma.

The technical success was defined as the secure fixation of the endograft, successful placement ensuring proper patency, and the absence of type I or III leakage within the first 24 hours. Clinical success was defined as successful

placement of the endovascular device at its intended site without complications such as type I or type III leak, graft infection or thrombosis, aneurysm enlargement (diameter >5 mm or volume >5 mL), aneurysm rupture, or death.

Renal dysfunction was defined as elevation of serum creatinine concentration more than 25% or 0.5 mg/dL (44 mmol/L) within 48 hours.

Secondary interventions to correct or prevent possible complications were also performed through endovascular procedures such as proximal cuff and stent implantation, distal lengthening implantation, catheter-based thrombolysis, iliac angioplasty, embolization of aortic branches, with coil and/or adhesive. When surgical intervention was required, open surgery was performed immediately.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as the mean ± standard deviation or median [minimum-maximum (min.-max.)], while categorical variables are expressed as numbers and percentages.

RESULTS

There were 54 octogenarian patients diagnosed with AAA who applied to our clinic. EVAR was applied to 36 patients. The mean age of the octogenarian patient group in our study was 84 (80-91) years. Patients are mostly male (83.3%). Average body mass index was 28.1 (19.3-42.2). We observed that most of the patients smoke (58.3%). When it comes to accompanying diseases, most of the patients had CAD (55.5%) and almost all of them had hypertension (88.9%). Fourteen patients (38.9%) who presented to our clinic were symptomatic. Eight of them (22.2%) were presented with a pulsatile mass in their abdomen. Atypical abdominal pain was present in 6 patients (16.7%) (Table 2).

The procedure was performed under general anesthesia in all patients. One unit of erythrocyte suspension (ES) was used in patients. In one patient, graft interposition was applied to the common femoral artery due to calcification during surgical opening of the femoral artery. In addition, 3 units of ES were applied because of concomitant CAD. When the abdominal aneurysm diameters were measured, it was seen that it was 7 cm and above in 13 patients (36.1%). Type 1 endoleak was detected in 2 patients, and type 2 endoleak in 2 patients. The iliac stent was extended in 2 patients with type 1 endoleak. Patients with type 2 endoleak were followed up without any extra procedures. No patients needed open surgery or experienced mortality (Table 3).

The procedure was completed successfully in all patients. Eight patients (22.2%) needed inotropes to avoid

Table 3. Procedural factors for octogenarians undergoing EVAR

		Median (min.-max.)	n	%
Intraoperative factors				
	Anesthesia			
	General		36	100
	Spinal		0	0
	Local		0	0
	Estimated blood loss, mL	150 (50- 300)		
	RBC transfused, U	1 (0 - 3)		
	Total procedure time, m	110 (80- 220)		
AAA maximum diameter, mm		6.1 (5-8.6)		
	<7cm		23	63.9
	>7cm		13	36.1
EVAR technical factors				
	Graft body diameter,mm	136 (96-172)		
	Endoleak		4	11.1
	Conversion to open repair		0	0
	Concominant procedure		2	5.5
		Stenting	2	5.5
Peroperative mortality			0	0

RBC: Red blood cell, AAA: Abdominal aortic aneursym, EVAR: Endovascular aortic repair

hypotension as they had CAD. A transient ischemic attack developed in 1 patient. Three patients (8.3%), after arterial ischemia developed in the leg where the main body of stent was placed, nedeed embolectomy. Maceration developed at the local wound site in 5 patients. Three of these 5 patients had hematoma at the intervention site. Acute renal failure did not develop in any patient. Intubation time was prolonged in 2 patients (5.5%), and in these patients, lung infection due to pneumonia developed. During follow-up computed tomography scans of 2 patients with type 2 endoleak, it was observed that there was no endoleak on the 30th day. There was no mortality in the 30-day ollow-up (Table 4).

All patients were evaluated on the post-operative 2nd and 30th days according to the Karnofsky quality of life and performance status scale (Table 5). The patient, who developed a transient ischemic attack and was extubated on the 2nd day, needed help with mobilization during his intensive care stay. All other patients were able to provide their own self-care. Patients often had symptoms because of the femoral incision wound. Considering the follow-up controls on the 30th postoperative day, no complications were observed in 32 patients. In two patients, there was a hematoma at the femoral wound site. The hematoma in 1 patient was treated surgically. Improvement was observed in Karnofsky scoring both on the 2nd postoperative day and on the 30th day with all patients.

DISCUSSION

The fact that AAA patients are mostly asymptomatic creates difficulties in diagnosing the disease and determining its frequency. However, it is known that AAA increases with age. In addition, considering both the European and American populations, it is predicted that the elderly population is gradually increasing and the octogenarian population will be more than 2% of the society in the future. Therefore, we believe that AAA patients will be encountered more in daily practice. Therefore, it is important to determine the adequate treatment for elderly patients. In this study, we aimed to evaluate our early results, in the octogenarian population to whom we applied EVAR.

The most feared and lethal clinical outcome in AAA is ruptured AAA (13). We face a greater risk of rupture with advancing age (14). Therefore, it is very important to closely monitor the clinical picture of patients with AAA. Options for treatments in patients with AAA are medical treatment, open AAA repair, and endovascular treatment. While determining this type of treatment, the diameter of the aneurysm, the anatomical features of the area with the aneurysm, and the accompanying comorbidities are taken into consideration (15). In the octogenarian AAA patient group, there is hesitance to perform an interventional procedure due to the high risk of mortality. The presence of other risk factors accompanying octogenarian patients with AAA has a negative effect on mortality and morbidity. Therefore, it is important to accurately assess the risk of AAA

Table 4. Perioperative outcome and complications

		Median (min.-max.)	n	%
Morbidity				
Techical success			36	100
Inotrop required			8	22.2
All comlications				
	Myocardial ischemia		0	0
	Stroke		1	2.8
	Intestinal ischemia		1	2.8
	Arterial ischemia		3	8.3
	Renal		0	0
	Pulmonary		2	5.5
	Access-site hematoma		3	8.3
	ICU duration, day	1 (1-4)		
	Total stay time, day	4 (3-8)		
Endoleak in 30 days			0	0
Mortality in 30 days			0	0

Min.-max.: Minimum- maximum, ICU: Intensive care unit

Table 5. Preoperative, postoperative 2nd day and 30th day Karnofky Scale

Karnofsky Performance Status Scale	Rating (%)	Patients number (Pre-op)	Patients number (2nd day)	Patients number (30th day)
Normal no complaints; no evidence of disease	100	14	18	24
Able to carry on normal activity; minor signs or symptoms of disease	90	10	7	6
Normal activity with effort; some signs or symptoms of disease	80	8	6	2
Cares for self; unable to carry on normal activity or to do active work	70	3	3	3
Requires occasional assistance, but is able to care for most of his personal needs	60	1	1	1
Requires considerable assistance and frequent medical care	50	0	1	0
Disabled; requires special care and assistance	40	0	0	0
Severely disabled; hospital admission is indicated although death not imminent	30	0	0	0
Very sick; hospital admission necessary; active supportive treatment necessary	20	0	0	0
Moribund; fatal processes progressing rapidly	10	0	0	0
Dead	0	0	0	0

rupture and the mortality risk of performing the procedure on these patients (16). In a study comparing patients who underwent EVAR and patients who received best medical treatment, 4-year survival was 97% in the EVAR group, while it was 67% in the bone marrow transplant (BMT) group. In the EVAR group, 78% of patients were without major adverse events, compared to 28% in the BMT group (17). In our study, the EVAR procedure was successfully applied to 36 octogenarian patients who were anatomically suitable and had no access problems. No mortality in the 1-month period was observed. Transient ischemic attack occurred in 1 patient, without any sequelae. We like other studies in the literature observed that EVAR reduces mortality due to aneurysm in high-risk patients compared to BMT.

In a study of 3.1 million patients, risk factors for AAA were found to be smoking, overweight, male sex, family history, hypertension, and advanced age (18). Non-steroidal anti-inflammatory use, and COPD, and cardiovascular disease were evaluated as independent risk factors for AAA. It was also found that the use of statins reduced the growth of aneurysm diameter by 1.1 mm/year (19). In our study, the risk factors were hypertension 88.9%), smoking (58.3%), male gender (83.3%), CAD (55.5%) as similar to literature. In addition, most patients are prescribed anti-hypertensive, American Society of Anesthesiologists, and statins due to CAD.

Anatomical evaluation should be performed in all patients presenting symptomatic or asymptomatic AAA. To perform the EVAR procedure, anatomical evaluation should be done before making an EVAR decision. The feasibility of EVAR becomes technically difficult or even impossible in aneurysms involving renal arteries or visceral organ branches, or in the case of an aneurysm with a very large sac, a short, and an angled neck. In addition, an effective physical examination and preliminary evaluation should be performed to assess access in AAA patients. In the absence of suitability, open surgery or BMT should be considered primarily for these patients (20,21). In our study, open surgery was performed in 4 patients, and 14 patients were followed up with BMT, since the EVAR procedure was not applicable for the 18 patients over the age of 80 who applied to our clinic. As a result of the preoperative evaluation, 36 patients were found to be suitable for the EVAR procedure and the technique was successfully applied to all 36 patients.

The effects of anesthetic method on the mortality and morbidity of the patients while the EVAR procedure is being performed are known. The EVAR procedure can be performed under general anesthesia, local anesthesia, or local combined with sedation. The general condition of the patients and whether the procedure is urgent or elective are the parameters that determine the choice of anesthesia. The fact that the octogenarian patient group is considered to be at high risk perse and that additional pathologies frequently accompany these patients leads to the recommendation that many guidelines and current studies suggest that the appropriate anesthetic option is local or local anesthesia with sedation (22,23). In our study, all procedures were done under general anesthesia. Risk factors were evaluated preoperatively and 5 (8.3%) patients were evaluated as moderate COPD. EVAR was performed under general anesthesia with these 5 patients. Intubation time was prolonged in 2 (5.5%) of these patients. Although

EVAR was applied under general anesthesia in all patients in our study, we propose that choosing the appropriate anesthesia as local or local combined with sedation would be less risky in terms of pulmonary problems, especially in patients who have insufficient lung capacity.

Conversion to open surgery as a treatment option should be ready for any complications that may occur during EVAR procedure. If rupture occurs, the patient should be operated on urgently. When type 1 endoleak is present, it is also important to perform elective re-intervention or open surgery. We know that the mortality of patients treated as urgent is 10 times higher than elective patients (24). In a study that reviewed 13 articles, mortality rates in the case of conversion to open surgery in the early period ranged from 0% to 28.5%. Mortality was observed to be approximately 10% in patients who underwent open surgery in the late period (25). There was no perioperative mortality in our study. In addition, there were no complications that required conversion to open surgery in the early period. Interventional treatment was applied to the endoleak formed during the procedure.

In the octogenarian population, intensive care and hospital stays are longer compared to those of younger patients with the same disease. We know that patients who underwent open surgery also experience longer stays in intensive care. Prolonged hospitalizations have negative effects both on patients and on cost-effectiveness. The most valuable result of endovascular treatment is the significant reduction in early mortality. Additionally, the duration of intensive care and hospitalization is shorter with endovascular treatment (26). In our study, the length of stay in the intensive care unit was 1 (min.: 1-max.: 4) days, and the median value of the total hospitalization was 4 (min.: 3, max.: 8) days. The most important factor prolonging hospitalization time was COPD. Shortening these lengths of stay will have positive effects on both patients and cost-effectiveness.

Although open surgery is always the gold standard for AAA, it always carries the risk of mortality and morbidity (27). The high comorbidity of octogenarian patients and the high fragility of these patients further increase the risk of mortality and morbidity. There are many studies comparing short and long-term results of open surgery and EVAR procedure in elderly patients (28,29). When we look at the short-term results of meta-analyses, we find that the mortality rates of EVAR are lower than those of open surgery. On the other hand, analyzing the 10-year long-term results, the data indicates that the mortality of EVAR and open surgery are similar (30). Although the superiority of EVAR was accepted when short-term mortality rates were evaluated in most of the studies; long-term mortality was higher in the EVAR group (30). In our study, no mortality was observed in any of the 36 patients who were followed up in the short term.

Scorings related to performance status (such as Karnofsky scoring) are used to assess patients' general condition and quality of life (30). These scores are frequently used in studies and have been gradually incorporated into cardiovascular surgery. It has been observed in many studies of both cardiac and non-cardiac surgery that the postoperative Karnofsky score shows a significant decrease compared to the preoperative score (30). Incision-related pain and metabolic stress caused by the operation are factors that impair the quality of life of patients in the early postoperative period of open surgery. However, rapid mobilization and recovery can be achieved in patients after endovascular procedures. In our study, endovascular treatment in octogenarian patients led to a high Karnofsky score even on the second postoperative day.

CONCLUSION

EVAR, which has equal success with open surgery in patients with AAA in the octogenerian, will significantly reduce operative morbidity, intensive care unit and hospital stay and cost when performed in an experienced and high-volume center. In addition, we believe that these patients who are Octogenerians imp

rove their performance more quickly.

ETHICS

Ethics Committee Approval: This study University of Health Sciences Türkiye, Bakırköy Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2022-17-09, date: 05.09.2022).

Informed Consent: Since this study was a retrospective study, patient consent was not required.

FOOTNOTES

Authorship Contributions

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

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):207-214
DOI: 10.4274/BMJ.galenos.2024.2024.3-4

Research

Aggregate Index of Systemic Inflammation and Systemic Inflammatory Response Index: Could be Potential Biomarkers to Monitor Bipolar Disorder Patients? An Observational Study

Sistemik Enflamasyonun Toplam İndeksi ve Sistemik Enflamatuvar Yanıt İndeksi; Bipolar Bozukluk Hastalarını İzlemek için Potansiyel Biyobelirteçler Olabilir mi? Gözlemsel Bir Çalışma

Ece Büyüksandalyacı Tunç[1], Hidayet Ece Arat Çelik[1], Burcu Kök Kendirlioğlu[1], Esma Çörekli Kaymakçı[1], Hatice Begüm Çiftçi[3], Şevin Demir[2], Suat Küçükgöncü[1]

[1]Maltepe University Faculty of Medicine, Department of Psychiatry, İstanbul, Türkiye
[2]Maltepe University Faculty of Medicine, Department of Family Medicine, İstanbul, Türkiye
[3]Manisa Salihli State Hospital, Medical Doctor, Manisa, Türkiye

ABSTRACT

Objective: Bipolar disorder (BD) is a severe psychiatric disorder characterized by recurrent episodes of mania and depression. Studies have reported the involvement of inflammatory processes in the pathophysiology of BD. This study aims to demonstrate that certain inflammatory markers are elevated in BD patients and to highlight their potential for use in diagnosis, prognosis, and treatment monitoring.

Methods: This study included 57 BD patients and 121 healthy controls (HC). All participants underwent a complete blood count. Subsequently, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) values were calculated. The ethics committee approval for the study was obtained from Maltepe University Faculty of Medicine on January 19, 2022, number 2022/900/02.

Results: The NLR, mean platelet volume (MPV), red cell distribution width (RDW), AISI, and SIRI values were higher in BD patients compared to HC. No significant differences were found in MLR, PLR, and SII levels between the BD and HC groups.

Conclusion: Higher NLR, MPV, RDW, AISI, and SIRI values in BD patients than HC suggest increased inflammatory processes in BD. NLR, MPV, RDW, SIRI, and AISI are believed to be involved in the pathophysiology of BD and hold potential as biomarkers for monitoring disease prognosis and treatment efficacy. To further understand the underlying mechanism of BD, additional longitudinal studies are needed to determine how BD impacts inflammatory processes.

Keywords: Bipolar disorder, neutrophil to lymphocyte ratio, mean platelet volume, systemic inflammatory response index, aggregate index of systemic inflammation, erythrocyte indices, inflammation

ÖZ

Amaç: Bipolar bozukluk (BB), tekrarlayan mani ve depresyon atakları ile karakterize ciddi bir psikiyatrik bozukluktur. Çalışmalar, BB'nin patofizyolojisinde enflamatuvar süreçlerin rol oynadığını bildirmektedir. Bu çalışma, BB hastalarında belirli enflamatuar markerların yükseldiğini göstermeyi ve bu markerların tanı, prognoz ve tedavi izleminde kullanılma potansiyelini vurgulamayı amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmaya, 57 BB hastası ve 121 sağlık kontrol (SK) dahil edilmiştir. Çalışmaya katılan katılımcılardan tam kan örneği alındı. Ardından, nötrofil-lenfosit oranı (NLR), monosit-lenfosit oranı (MLR), trombosit-lenfosit oranı (TLR), sistemik inflamasyon indeksi (SII), sistemik

Address for Correspondence: Ece Büyüksandalyacı Tunç MD, Maltepe University Faculty of Medicine, Department of Psychiatry, İstanbul, Türkiye
E-mail: dr.ecetunc@gmail.com **ORCID ID:** orcid.org/0000-0002-6358-4643

Cite as: Büyüksandalyacı Tunç E, Arat Çelik HE, Kök Kendirlioğlu B, Çörekli Kaymakçı E, Çiftçi HB, Demir Ş. Et al. Aggregate index of systemic inflammation and systemic inflammatory response index: could be potential biomarkers to monitor bipolar disorder patients? an observational study. Med J Bakirkoy. 2025;21(2):207-214

Received: 16.03.2024
Accepted: 27.12.2024
Publication Date: 04.06.2025

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ÖZ

enflamatuar yanıt indeksi (SIRI) ve sistemik enflamasyonun toplam indeksi (AISI) değerleri hesaplandı. Çalışmanın etik kurul onayı Maltepe Üniversitesi Tıp Fakültesinden 19.01.2022 tarih, 2022 /900/ 02 no ile alınmıştır.

Bulgular: BB hastalarının NLR, ortalama trombosit hacmi (MPV), eritrosit dağılım genişliği (RDW), SIYI ve SIRI değerleri SK'e göre daha yüksekti. BB grubu ile SK arasında MLR, TLR ve SII seviyeleri arasında anlamlı bir fark yoktu.

Sonuç: BB hastalarında SK'e kıyasla daha yüksek NLR, MPV, RDW, AISI ve SIRI değerleri, BB'da artmış inflamatuvar süreçleri işaret etmektedir. NLR, MPV, RDW, SIRI ve AISI'nin, BB'un patofizyolojisinde yeri olduğu, ayrıca hastalığın prognozunu ve tedavinin etkinliğini izlemek için potansiyel biyobelirteçler olduğu düşünülmüştür. BB'nin temel nedenlerini daha iyi anlamak ve bozukluğun inflamatuvar süreçleri nasıl etkilediğini belirlemek için ek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Bipolar bozukluk, nötrofil-lenfosit oranı, eritrosit indeksleri, sistemik inflamatuar yanıt indeksi, sistemik enflamasyonun toplam indeksi, Ortalama trombosit hacmi, İnflamasyon

INTRODUCTION

Bipolar disorder (BD) is a severe mood disorder affecting millions worldwide, characterized by episodes of mania and depression. While genetic, environmental, and neurobiological factors are implicated in its etiology, growing evidence suggests that systemic inflammation and immunological abnormalities are crucial components in the pathogenesis of BD. According to studies, during manic and depressive episodes, patients with BD exhibit higher pro-inflammatory cytokines, acute-phase proteins, and immune activation markers (1). This inflammatory state may contribute to neuroprogression and mood symptoms. Various hypotheses have been proposed for how cytokines enter the central nervous system (CNS). Three potential mechanisms are the binding to cytokine-specific carrier molecules generated by the endothelium, the stimulation of vagal afferent pathways that transmit cytokine signals to various brain nuclei, and access to areas without a blood-brain barrier, such as circumventricular organs. Cytokines enter the CNS through one or more of these pathways, causing neuroinflammation (1,2). Focusing on various inflammatory markers is essential to better understand the inflammatory processes of BD. These markers play a critical role in monitoring the course of the disorder and assessing treatment responses. In particular, markers that reflect the level of systemic inflammation may help to elucidate possible mechanisms in the pathogenesis of BD. In addition, these inflammatory markers may vary depending on the clinical condition of the patients, allowing for the development of individualized treatment strategies. A closer look at some inflammatory markers and their effects on BD is needed (3).

The systemic inflammatory index (SII), the aggregate index of systemic inflammation (AISI), systemic inflammation response index (SIRI), neutrophil/ lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and platelet/lymphocyte ratio (PLR) values have been investigated for evaluating inflammatory dysregulation in long-term illnesses like cancer, diabetes mellitus and heart disease (4). White blood cell assays can quickly determine these values in a laboratory setting. Neutrophils serve as the initial line of defense of the immune system. However, lymphocytes are also essential for mediating adaptive immune reactions. Platelets affect immune response management, coagulation, and serotonin release in inflammatory conditions. Significantly, serotonin, in turn, elevates cytokine levels. Monocytes are a subset of leukocytes known for their pro-inflammatory effects (5).

According to the complete blood count, mean platelet volume (MPV) denotes the average size of platelets, and an increase in MPV is associated with inflammatory processes. An increase in MPV indicates that large platelets are being circulated, supporting the idea that MPV can indicate active inflammation. It has been identified as a new potential biomarker for diagnosing several diseases. These include neoplastic disease, cardiovascular diseases, inflammatory bowel diseases, cerebrovascular events, and neurodegenerative diseases (6,7). Since inflammation is also seen in BD, MPV might be a possible biomarker (8,9). Red cell distribution width (RDW), a measure of heterogeneity in the size of circulating red blood cells, is a percentage determined from the hemogram using the standard deviation (SD) of red blood cell volume divided by the mean corpuscular volume and expressed as a percentage. Increased RDW levels are linked to poor erythropoiesis or erythrocyte breakdown. Recent research has studied RDW as an inflammatory marker in several clinical disorders, such as rheumatoid arthritis, inflammatory bowel disease, colon cancer, and celiac disease (10). Higher RDW levels have been linked to chronic inflammatory disorders, and this increase might also present in BD (11)

NLR, a simple and affordable indicator of systemic inflammation, is calculated as the NLR ratio in peripheral blood. Higher NLR indicates an enhanced pro-inflammatory state and has been linked to various neuropsychiatric disorders, including BD. Recent studies have shown significantly higher NLR values in BD patients during manic

and depressive episodes, suggesting NLR may help assess mood states (8). PLR highlights the interaction between platelets, involved in coagulation and inflammation, and lymphocytes, which are essential for immune regulation. Higher PLR is a straightforward and effective measure of inflammation severity. High PLR has been observed in BD patients, especially during manic episodes, highlighting the potential role of platelet-mediated inflammation in the disorder (12). The MLR has also gained attention in BD research. Higher MLR has been associated with more severe manic symptoms, suggesting a possible link between monocyte-mediated inflammation and BD severity (3,12).

SII is calculated as SII=platelet count×NLR. SII has been reported to be associated with systemic inflammatory status and short-term adverse outcomes in patients with pancreatic cancer and acute ischemic stroke, and it potentially predicts an adverse prognosis in these patients (13,14). SII is also found to be a risk factor and a predictor for the development of depression in patients with diabetes mellitus (15). In BD, elevated SII has been associated with increased disease severity, suggesting a link between systemic inflammation and symptomatology (16,17). AISI is a relatively new index used to evaluate the relationship between inflammation and various disorders. AISI is calculated as neutrophil x platelet x monocyte/lymphocyte. This index provides a broader view of inflammation, allowing for a more comprehensive evaluation of the body's inflammatory response (4). In two thesis studies, AISI values were higher during the manic period of BD than during the depressive and euthymic periods, although healthy controls (HCs) were not included in these studies (18,19). SIRI is calculated as neutrophils × monocytes/ lymphocytes (20). High levels of SIRI appear to be a marker of chronic inflammation in various medical conditions (20,21). High SIRI levels may indicate worse depressive outcomes in treatment-resistant BD patients with significant depressive symptoms at baseline (20).

Research findings indicate that inflammatory parameters fluctuate in BD, and changes in these parameters may be related to the severity of manic or depressive symptoms. We hypothesized that inflammatory markers such as NLR, SIRI, AISI, and SII levels are elevated in BD patients compared to HC. Furthermore, the relationship between AISI and BD has not yet been sufficiently studied, and we hypothesized that these markers would be higher in the BD group than in HC. This study aims to explore the relationship between BD and the inflammatory markers discussed in the paper, and to contribute to the literature by identifying markers that can be used to monitor and treat BD, where inflammatory processes are active.

METHODS

This is a retrospective observational study. It included 57 patients diagnosed with BD who were hospitalized for treatment at the Maltepe University Faculty of Medicine, Department of Psychiatry, between 2013 and 2022. A total of 121 HCs were selected from individuals without psychiatric disorders who visited Maltepe University Faculty of Medicine, Department of Family Medicine, for routine health checks between 2020 and 2022. The diagnosis of BD was made by an experienced psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders 5 diagnostic criteria. The study was approved by the Clinical Research Ethics Committee of Maltepe University Faculty of Medicine (decision no: 2022 /900/ 02, date: 19.01.2022).

Participants

This study investigated individuals aged 18 to 65 and reviewed their past health data. Within the first 24 hours after admission, blood samples were collected from individuals admitted to the psychiatry inpatient clinic for 36 manic (63.2%) and 21 depressive (36.8%) episodes of BD. Individuals with a history of substance abuse, hypertension, diabetes mellitus, heart disease, autoimmune or inflammatory disorders, cancer, active infections, or individuals using medications that may affect the immune system were excluded from the study. Based on this criterion, 14 individuals were removed from the HC group, and eight were excluded from the BD group. Additionally, in the HC group, individuals suspected of having an acute or lifetime psychiatric disorder or alcohol or substance use disorder were excluded based on routine consultations with their primary care physician.

Statistical Analysis

Descriptive statistics included the mean, SD, median, minimum, maximum, frequency, and ratio values. The Kolmogorov-Smirnov test was used to assess the distribution of the variables. An independent samples t-test and the Mann-Whitney U test were used to analyze quantitative independent data, while the Chi-square test was employed for independent qualitative data. Data analysis was performed using the SPSS 28.0 software. A p-value of 0.05 was considered statistically significant, and the results of all tests were reported as the mean ± SD. According to the power analysis, the difference in group sizes did not affect the significance of our results.

RESULTS

Data from 57 BD patients (35 female, 22 male) and 121 HC (69 female, 52 male) were included in the study. The mean age was 37.5±8.3 years (median: 38.0) in BD patients

and 37.1±11.9 (median: 37.0) in the HC group. There was no significant difference (p>0.05) in age and gender distribution between the HC and BD groups. Neutrophils, monocytes, RDW, and MPV values were significantly higher (p<0.05) in the BD group compared to the HC group. Socio-demographic data and hemogram test results are shown in Table 1.

NLR, SIRI, and AISI values were significantly higher (p<0.05) in the BD group compared to the HC group, while lymphocyte, platelet, MLR, PLR, and SII showed no significant difference (p>0.05) between the two groups (Table 2). The comparison of NLR, SIRI, and AISI levels between the groups is shown in Figure 1.

DISCUSSION

The inflammatory system plays a crucial role in the onset and progression of BD, and numerous studies have been conducted on this topic. In our study, we observed that the BD group had higher neutrophil, monocyte, RDW, MPV levels, as well as NLR, AISI, and SIRI levels compared to the HC group. However, there were no statistically significant changes in lymphocyte and platelet levels, SII, PLR, and MLR. although NLR, PLR, and MLR have been studied extensively in BD patients, RDW, MPV, SII, AISI, and SIRI have rarely been investigated. In particular, the difference in AISI levels between BD and HC has not been studied before.

In a 2020 meta-analysis examining NLR levels in mood disorders, 11 studies were reviewed. NLR levels in BD were consistently higher than in HCs, regardless of whether the episodes were manic, depressive, or euthymic (22). BD patients in their first manic episode had significantly higher NLR levels than chronic patients (23). Additionally, compared to the remission period, BD patients in manic and depressive episodes showed higher NLR levels (3.24). Considering all these findings, the inflammatory response increases during the manic and depressive periods of BD, and NLR is a marker that can be monitored during treatment.

In this study, BD patients had considerably higher RDW values than HCs. RDW is a biomarker that measures the variation in red blood cell size and is commonly used to assess anemia and hematological illnesses. In recent years, increasing evidence has suggested that RDW is linked to

Table 1. Sociodemographic data and hemogram results of bipolar disorder patients and healthy controls

		Healthy control			Bipolar disorder			p-value	
		Median±SD/n-%		Median	Median±SD/n-%		Median		
Age		37.5±8.3		38.0	37.1±11.9		37.0	0.472	m
Gender	Female	69	57.0%		35	61.4%		0.580	X^2
	Male	52	43.0%		22	38.6%			
Neutrophil		4028.7±1216.1		3980.0	5118.0±2448.6		4800.0	**0.006**	m
Lymphocyte		2425.9±684.7		2360.0	2495.5±712.2		2480.0	0.416	m
Monocyte		603.9±199.0		590.0	675.3±207.2		660.0	**0.016**	m
Platelet		246.9±61.8		245.0	246.3±68.1		243.5	0.640	m
RDW		13.3±0.8		13.2	13.9±1.1		13.7	**0.001**	m
MPV		10.2±0.9		10.1	9.8±1.1		9.8	**0.014**	m

m: Mann-Whitney u test, X^2 chi-square test, RDW: Red cell distribution width, MPV: Mean platelet volume

Table 2. Values of inflammatory indices in bipolar disorder patients and healthy controls

	Healthy control		Bipolar disorder		p-value	
	Median.±SD/n-%	Median	Median.±SD/n-%	Median		
NLR	1.76±0.68	1.66	2.27±1.57	1.94	**0.003**	t
MLR	0.26±0.08	0.25	0.29±0.13	0.26	0.202	m
PLR	107.5±33.7	103.8	106.1±39.7	103.0	0.809	t
SII	433.2±196.2	398.9	580.0±501.1	448.6	0.211	m
SIRI	1072.6±566.9	960.5	1582.3±1224.6	1196.4	**0.017**	m
AISI	2744.1±1849.7	2201.0	4096.8±3758.2	2777.8	**0.038**	m

t: Independent samples t-test, m: Man-Whitney u test, X^2 Chi-square test, NLR: Neutrophil/ lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, PLR: Platelet/ Platelet/lymphocyte ratio, SII: Systemic inflammation index, SIRI: Systemic inflammation response index, AISI: Aggregate index of Systemic inflammation

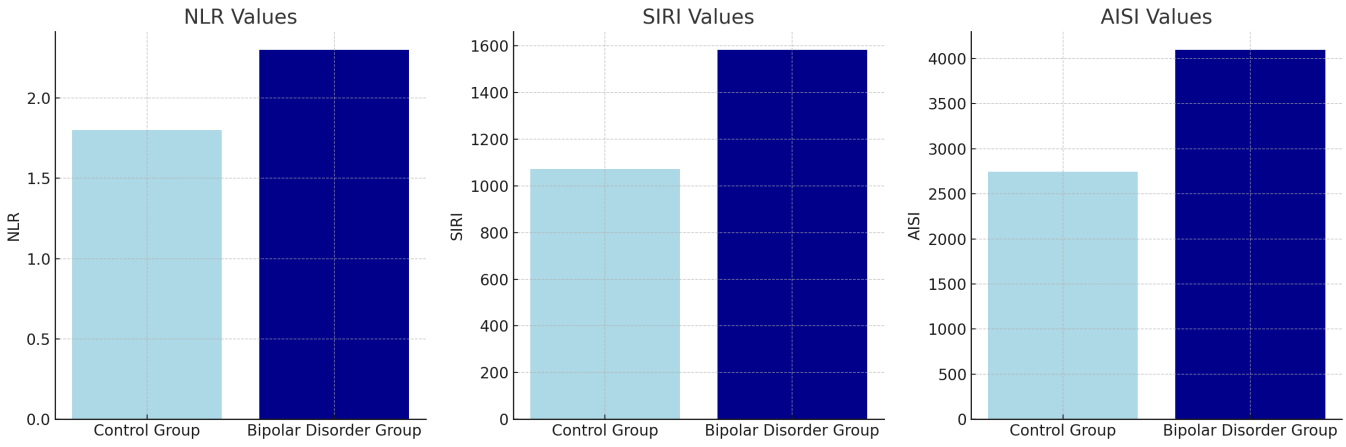


Figure 1. Comparison of NLR, SIRI and AISI levels of groups

NLR: Neutrophil/lymphocyte ratio, SIRI: Systemic inflammation response index, AISI: Aggregate index of systemic inflammation

systemic inflammation. Elevated RDW has been associated with chronic inflammatory diseases such as cardiovascular disease and it is believed that this rise may also occur in neuropsychiatric disorders like BD (11,25). Previous studies have found higher levels of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha in BD patients. These cytokines influence erythropoiesis and are thought to promote red blood cell size variability. Increased oxidative stress can damage red blood cell membrane integrity, leading to elevated RDW (26) Kirlioglu et al. (27) evaluated inflammatory markers based on complete blood counts in BD mania and mixed episodes, discovering a link between inflammation and hematologic parameters. In contrast to previous research, the investigation of RDW in BD suggests that can be employed as a biomarker of inflammatory processes.

To our knowledge, the relationship between BD and SIRI and AISI has not been adequately examined in the literature. AISI and SIRI are new indices that reflect the inflammatory and immune status. According to a study's finding, high SIRI levels may predict worse depressive outcomes in treatment-resistant BD patients with significant depressive symptoms at baseline (20). Another study found that SIRI correlates with endothelial dysfunction in BD patients during depressive episodes (28). A study comparing SIRI values between BD patients, schizophrenia patients, and HCs found that the SIRI levels were higher in both BD and schizophrenia patients than in HCs. In light of this, SIRI may be a useful inflammatory marker to distinguish these patients (17). AISI, a more recently developed inflammatory marker, has been studied less in general literature, and in psychiatry literature. AISI may also have other clinical applications in systemic pro-inflammatory diseases, such as cancer. White blood cell, neutrophil, monocyte, lymphocyte, and platelet counts alone in predicting four-year survival. Based on this, the presence and severity of inflammation seem to be directly proportional to the higher AISI values (29). As far as we know, the psychiatric studies on AISI are limited to two theses. According to the results of these studies, AISI values of BD patients during manic episodes were found to be higher than those during BD depressive and euthymic periods (18,19). While our study supports the results of these two theses, comparing BD patients to HC revealed a new finding. In light of all these data, it is thought that AISI could be used as an inflammatory marker and that it may be more specific to manic episodes. It would be appropriate to support these findings with more comprehensive studies. Considering the research in the literature, elevated AISI and SIRI are known to indicate prognostic features in inflammatory diseases. Similar results have been found in the limited number of studies conducted in BD so far, and it is thought that BD is an inflammatory disorder, with AISI and SIRI potentially serving as prognostic markers. Undoubtedly, there is a need for more studies with larger patient samples to explore the contributions of AISI and SIRI in monitoring treatment response and prognosis in BD.

Platelets, as a non-specific first-line inflammatory signal, along with platelet activation modulated by inflammatory mediators, P-selectin and neurotransmitters, can modify endothelial permeability, allowing neutrophils and macrophages to recruit more efficiently. Since MPV is associated with inflammation and affects both platelet count and function, elevated levels of MPV in BD patients have been proposed as potential indicators of

inflammation. Some studies have demonstrated increased MPV in BD patients (7-9,30,31), while others have shown uncertain or less significant results (11,27). This is most likely due to methodological differences in the research, patient group differentiation, and varying stages of the disease. Therefore, more studies on this subject are needed. PLR can be used to predict the inflammatory response in mood disorders. A meta-analysis found that patients with BD had higher PLR levels than controls (22). However, in the current investigation, no significant difference in platelet count or PLR values was detected between the groups. Other studies have reported altered platelet count and PLR levels in mood disorders, but their findings are inconsistent (26). Studies found NLR to be a more consistent marker of inflammation when compared with PLR. Hence, PLR may not be considered a reliable marker for BD.

Our research showed that monocyte levels in BD patients were considerably higher than those in HC, but there was no significant difference in MLR levels. When examining monocyte and MLR levels, as seen in many psychiatric disorders, BD patients may have higher circulating monocytes due to enhanced immune gene expression and excess production of cytokines linked with monocytes/macrophages. Given that microglial activation could be part of the systemic cytokine activation and the mononuclear phagocyte system, the high MLR during manic episodes in BD might be interpreted as a peripheral marker of brain inflammation (32). However, more understanding of this measure in BD is still needed. In contrast to our findings, studies that examined MLR in BD patients found considerably higher MLR in hypomanic or manic BD groups than in depressive BD groups, even though these patients were not compared to HC (12,22). The observed monocyte levels, despite their significance, did not show a significant difference, which could be due to the relatively small sample size, while MLR levels were not significant in our study. Further research using similar methods is needed to clarify the role of monocytes in BD episodes.

Previous studies have emphasized the significance of SII in predicting the prognosis of various physical illnesses, including tumors (33) and psychiatric disorders (34). Wei et al. (17) found that BD patients exhibited higher SII levels than HC. Furthermore, they discovered that SII values were significantly higher in BD patients experiencing manic episodes than in depressive episodes (35). On the other hand, one study found that while SII levels were elevated in BD patients, there was no significant difference between manic or depressive episodes (16). It has been reported that, in BD, SII levels do not significantly differ from those in HC (36). Additionally, some studies report that SII is higher over the manic episode than the depressive period in BD (17). Since we did not separately compare patients in manic, and depressive episodes in this study, we believe this may explain our results. Prospective studies aimed at distinguishing the episodes should be conducted on this subject.

Study Limitations

Our study would benefit from a larger sample size. Therefore, the results of our research should not be generalized to all BD patients. Another limitation is the study's retrospective nature, which means that patients were not monitored for inflammatory markers during remission. One significant limitation is that we evaluated all episodes as a group, not separately as manic and depressive episodes. Future studies could address this by separating the episodes. Furthermore, while we adjusted for potentially confounding factors such as age and sex, other variables, such as body mass index, medication use, and lifestyle factors, may influence inflammatory markers. Future studies should also consider how treatments and the resolution of manic or depressive episodes impact inflammatory markers in the bloodstream.

Conclusion

Systemic inflammation and immune dysregulation are critical factors in the pathophysiology of BD. NLR, MPV, RDW, AISI, and SIRI are promising biomarkers for BD that can help in understanding the disorder's pathophysiology, diagnosing it, evaluating its prognosis, and monitoring treatment. However, further research is needed to validate their clinical utility, establish standardized cutoff values, and clarify the complex relationships between inflammation and BD. Integrating these biomarkers into clinical practice may offer a more personalized and practical approach to managing this complex psychiatric disorder.

ETHICS

Ethics Committee Approval: This study Maltepe University Clinical Research Ethics Committee (decision no: 2022/900/02, date: 19.01.2022).

Informed Consent: This is a retrospective observational study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: E.B.T., H.E.A.Ç., B.K.K., E.Ç.K., H.B.Ç., Ş.D., S.K., Consept: E.B.T., H.E.A.Ç., B.K.K., Ş.D., Design: E.B.T., H.E.A.Ç., B.K.K., Data Collection or

Processing: E.B.T., E.Ç.K., H.B.Ç., Ş.D., S.K., Analysis or Interpretation: E.B.T., H.E.A.Ç., H.B.Ç., S.K., Literature Search: E.B.T., Writing: E.B.T., H.E.A.Ç., B.K.K., E.Ç.K.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):215-220
DOI: 10.4274/BMJ.galenos.2025.2024.4-4

Research

Evaluation of Non-invasive Parameters for the Detection of Bladder Outflow Obstruction in Patients with Symptomatic Benign Prostatic Hyperplasia

Semptomatik Benign Prostatik Hiperplazili Hastalarda Mesane Çıkış Obstruksiyonunun Tespitinde Non-invazif Parametrelerin Değerlendirilmesi

Yusuf Arıkan[1], Ubeyd Sungur[2], Hakan Polat[2], Mehmet Zeynel Keskin[1]

[1]University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital, Clinic of Urology, İzmir, Türkiye

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

ABSTRACT

Objective: To identify sonographic and morphological parameters of the prostate and bladder that predict bladder outlet obstruction (BOO) in benign prostate hyperplasia patients with lower urinary tract symptoms (LUTS).

Methods: The data of patients evaluated for LUTS between 2019-2023 were retrospectively screened. Following the inclusion and exclusion criteria, 320 patients were included in the study. The patient's medical history, physical examination, laboratory findings, ultrasonography findings, and urodynamic examination results were recorded. In the urodynamic examination, participants were divided into two groups: Group 1 (n=180) with a BOO index (BOOI) ≥40, and Group 2 (n=140) with a BOOI <40. These two groups were then compared.

Results: There was no statistical difference in age and international prostate symptom score results between the two groups. In univariate analysis, maximal flow rate (Qmax), post-void residual urine volume, serum Prostate specific antigen, intravesical prostate protrusion (IPP), ultrasound estimated bladder weight, and bladder wall thickness were found to be significant predictors, while in multivariate analysis Qmax and IPP were determined as significant predictive factors.

Conclusion: IPP and Qmax can be used as non-invasive tests to predict BOO in patients evaluated with LUTS.

Keywords: Benign prostatic hyperplasia, bladder outflow obstruction, non-invasive parameters, ultrasonography, urodynamic

ÖZ

Amaç: Alt üriner sistem semptomları (AÜSS) olan iyi huylu prostat büyümesi hastalarında mesane çıkış obstrüksiyonunu (MÇO) öngören prostat ve mesanenin sonografik ve morfolojik parametrelerini belirlemek.

Gereç ve Yöntem: 2019-2023 yılları arasında AÜSS açısından değerlendirilen hastaların verileri retrospektif olarak tarandı. Dahil etme ve dışlama kriterleri sonrasında 320 hasta çalışmaya dahil edildi. Hastaların medikal öyküsü, Fizik muayene, laboratuar, ultrasonografi bulguları ve ürodinamik inceleme sonuçları kaydedildi. Ürodinamik incelemede MÇO ≥40 olanlar Grup 1 (n=180), MÇO <40 olanlar Grup 2 (n=140) olarak ayrılarak bu iki grup karşılaştırıldı.

Bulgular: İki grup arasında yaş ve uluslararası prostat semptom skoru sonuçları arasında istatistiksel anlamlı fark izlenmedi. Tek değişkenli analizde maksimal akım hızı (Qmax), İşeme sonrası rezidü idrar, serum Prostat Spesifik Antijen, intravezikal prostat uzanımı (IPP), ultrasonla hesaplanmış mesane ağırlığı ve mesane duvar kalınlığı anlamlı prediktörler olarak bulunurken Çok değişkenli analizde Qmax ve IPP anlamlı olarak predikte edici faktörler olarak belirlendi.

Sonuç: AÜSS ile değerlendirilen hastalarda mesane çıkış obstruksiyonunu predikte etmek için IPP ve Qmax non-invazif testler olarak kullanılabilir.

Anahtar Kelimeler: Benign prostat hiperplazisi, mesane çıkış tıkanıklığı, non-invazif parametreler, ultrasonografi, ürodinami

Address for Correspondence: Yusuf Arıkan MD, University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital, Clinic of Urology, Izmir, Türkiye
E-mail: dryusufarikan@gmail.com **ORCID ID:** orcid.org/0000-0003-0823-7400

Cite as: Arıkan Y, Sungur U, Polat H, Keskin MZ. Evaluation of non-invasive parameters for the detection of bladder outflow obstruction in patients with symptomatic benign prostatic hyperplasia. Med J Bakirkoy. 2025;21(2):215-220

Received: 25.06.2024
Accepted: 27.01.2025
Publication Date: 04.06.2025

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INTRODUCTION

Bladder outlet obstruction (BOO) is a complex condition influenced by various factors. The factors contributing to BOO include detrusor contractility, smooth muscle remodeling, reduced blood flow, and mechanical stress. The diagnosis of BOO benign prostatic hyperplasia (BPH) has been one of the controversial topics in urology (1). Various methods, including questionnaires evaluating symptoms, urine flow rate and post-void residual (PVR) urine volume were used for the differential diagnosis of BOO. However, these tests are not specific for BOO (2).

Pressure flow studies (PFS) are considered to be the most useful tests in the diagnosis of BOO. However, its use in daily practice is limited because it is not easy to perform, it is not available in every clinic, there is a risk of infection related to the procedure, and it is invasive (3). Many researchers have investigated the accuracy of the diagnosis of BOO/BPH with intravesical prostate protrusion (IPP), bladder wall thickness (BWT), detrusor wall thickness, ultrasound estimated bladder weight (UEBW), prostate volume (PV), and transitional zone volume (TZV) measurements of bladder and prostate sono-morphologic parameters (4-6).

The aim of this study was to determine the sonographic and morphological parameters of the prostate and bladder that predict BOO in BPH patients with lower urinary tract symptoms (LUTS).

METHODS

This study was approved by approved by University of Health Sciences, Türkiye İzmir Tepecik Education and Research Hospital Non-interventional Research Ethics Committee (decision no: 2024/ 02-16, date: 04.03.2024). All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

All clinical data were collected retrospectively from patients evaluated for LUTS between 2019-2023. All 869 patients with LUTS were included in this study. The patients included in the study were those with an indication for urodynamics according to the European Association of Urology guidelines and who had completed a urodynamic study: (a) before to invasive treatment or when further evaluation of the underlying pathophysiology of LUTS is required, (b) men unable to void more than 150 mL and considering invasive treatment, (c) men considering surgery with bothersome predominantly voiding LUTS and Qmax >10 mL/s, (d) men with predominantly voiding LUTS and post-voiding residual >300 mL, and (e) men over the age of 80 years considering invasive treatment (7). Exclusion criteria included being under 50 years of age, having urethral stricture, having prostate or bladder malignancy, having a history of previous prostate surgery or pelvic radiation, having any neurological disorder that may affect bladder function, lacking urodynamic evaluation, and declining to participate in the study. After applying the exclusion criteria, the data of 320 patients were analyzed retrospectively.

A detailed medical history and a physical examination were performed on all patients with LUTS. LUTS evaluation was performed using the international prostatic symptom score (IPSS). Physical examination included digital rectal and neurological examinations. Urinalysis, creatinine, and prostate-specific antigen (PSA) were ordered as laboratory tests. A uroflowmetry test was ordered and peak urine flow rate (Qmax) and PVR were determined with this test. Pelvic ultrasonography and PFS were performed in patients who fulfilled the inclusion criteria.

Urodynamic evaluation was performed using the Solar Video Urodynamic system according to the recommendations of the International Society of Incontinence Good Urodynamic Practices protocol (8). Before urodynamic examination, the urine culture was sterile in all patients, and then the procedure was performed. BOO was determined using the BOO index with the following formula: BOOI=PdetQmax-2 Qmax from PFS (9).

All ultrasonography (USG) parameters were measured by a single operator. USG was performed when the bladder volume was between 100-200 mL. Bladder volume was assessed to calculate volume, using the prostate ellipsoid method, as the product of length, width, and height, multiplied by a correction factor (0.52).

The BWT hypoechoic layer was measured using a 7.5 MHz linear probe. The UEBW was then determined by combining the estimated BWT with the bladder volume (10). Following this, trans-rectal USG was performed simultaneously in the left lateral decubitus position. A sagittal image was obtained transrectally, and IPP was measured as protrusion from the bladder neck. IPP was divided into 3 grades according to its length: Grade 1 if 5 mm, Grade 2 if 5-10 mm, and Grade 3 if >10 mm. TZV was calculated by measuring its dimensions in both transverse and sagittal views, transrectally.

Patients were divided into two groups: those with BOO index (BOOI) ≥40 and those with BOOI <40. We compared these two groups in terms of age, Qmax, voided volume, post-micturition residual (PMR), serum PSA level, PV, IPSS, and sonographic non-invasive parameters.

Statistical Analysis

Statistical data analyses were performed using IBM SPSS Statistics for Windows version 25 (IBM Corp., Armonk, NY, USA). Data are presented as the mean ± standard deviation, the median, interquartile ranges, or frequency (%). The chi-square test (Continuity Correction, Fisher's exact test, or Pearson chi-square) was used to compare the categorical variables. Multivariable logistic regression models were constructed using the stepwise backward Wald method. A $p<0.05$ was considered significance level of statistically significant.

RESULTS

After applying the inclusion and exclusion criteria, 320 patients were included in the study. Patients with BOOI ≥40 were classified as Group 1 and patients with BOOI <40 were classified as Group 2. The mean age of patients in Group 1 and Group 2 was 70.1 and 68.1 years, respectively. Among the uroflowmetry parameters, Qmax and voiding volume were found to be statistically lower in Group 1 patients in univariate analyses. There was no difference between the groups in terms of PMR. There was no statistical difference in cystometric capacity between the two groups. Among the non-invasive USG parameters, BWT, UEBW, and IPP were statistically higher in Group 1 patients in univariate analysis. Univariate analyses of patients in Group 1 and Group 2 are shown in Table 1.

When the factors predicting BOO status were analyzed, 51.8% of the cases were detected in patients over 70 years of age. Patients with Qmax <10 constituted 47.5% of the population. IPP >10 mm was detected in 73.8% of patients. Other factors predicting BOO are shown in Table 2.

In multivariate analyses, Qmax and IPP were found to be statistically significant. It was determined that voiding volume, PSA level, PV, UEBW, and BWT values did not predict BOO status. Multivariate analysis results are shown in Table 3.

DISCUSSION

In patients presenting with LUTS, differentiating diseases presenting with symptoms similar to BPH and determining the severity of symptoms is an important step. Uroflowmetry and PVR are non-invasive tests for BPH and can provide insight into voiding dysfunction. However, non-invasive tests are not always sufficient to decide the most appropriate treatment option. Invasive tests have been used to determine the severity of BPH in individual patients. (11,12).

A comprehensive assessment of LUTS necessitates the evaluation of voiding pressure and Qmax through the employment of PFS. Despite the proven reliability of PFS in detecting BOO, this diagnostic method is characterized by invasiveness and high expenses. Additionally, its complexity has made it difficult to use routinely in clinical practice. Therefore, patients with a presumed diagnosis of LUTS/BPH are given an empiric first-line treatment protocol and PFS is only performed when initial medical therapy fails, or surgery is indicated. The utilization of a standardized treatment plan based on clinical experience is prone to overtreating individuals with mild BOO and those experiencing LUTS due to causes other than BOO. Moreover, in cases where BOO is the primary factor contributing to LUTS, administering empirical treatment could mask symptoms, leading to silent obstruction. These factors have expedited the progress in creating straightforward and non-invasive diagnostic tests as substitutes for PFS (13-15).

BPH is recognized as linked to structural alterations in both the prostate gland and the urinary bladder. These structural modifications can be conveniently assessed using pelvic USG (16). In this study, transrectal USG was used to better evaluate PV and TZ. We did not find any correlation between PV and BOO in our study.

Table 1. Comparison of demographic data, laboratory and ultrasonographic findings between groups

Parameters (mean±SD)	Group 1 (n=180)	Group 2 (n=140)	p-value
Age (year)	70.1±8.6	68.1±9.2	0.212
Qmax (mL/sec)	9.3±3.1	12.6±5.2	**0.001**
Voided volume (mL)	220.5±114.3	302.2±127.7	**0.001**
Postvoid residual volume (mL)	92.4±56.9	80.6±50.3	0.312
Maximal cystometric capacity (mL)	346.5±110.5	386.2±106.1	0.256
BOOI	64.8±23.1	16.8±11.6	**0.001**
PSA (ng/dL)	4.4±3.1	2.1±1.8	**0.001**
Prostate volume (mL)	55.9±32.1	39.6 ± 8.5	**0.001**
IPSS (sum)	19.3±8.8	19.8±8.0	0.089
Voiding symptom	10.9±5.8	11.7±5.5	0.516
Storage symptom	8.3±3.9	8±3.7	0.225
Quality of life	4±1.3	4.2±1.4	0.678
TZI	0.6±0.3	0.6±0.4	0.829
BWT (mm)	6.1±3.1	3.4±2.8	**<0.001**
UEBW (g)	34±13	24±12	**<0.001**
IPP (mm)	10.8±7.2	7.2±5.8	**<0.001**

Qmax: Maximal flow rate, BOOI: Badder outlet obstruction index, IPSS: International Prostatic Symptom Score, TZI: Transitional zone index, BWT: Bladder wall thickness, UEBW: Ultrasound estimated bladder weight, IPP: Intravesical prostate protrusion

A PSA level blood test is required for patients with BPH, and it should be further investigated if values exceed certain thresholds (16). In our study, the possibility of BOO in patients with PSA >4 was found to be statistically significant in univariate analyses, but no association was detected in multivariate analyses.

Uroflowmetry and PMR tests are among the tests ordered in the basic evaluation of patients presenting with LUTS. These tests guide the clinician in terms of obstruction (17). Considering the relationship between BOO and Qmax, low Qmax values were found to be significant for indicating urinary obstruction in a prospective study by Affusim et al. (18). In our study, a relationship was found between Qmax and BOO in multivariate analyses. No correlation was observed between voiding volume and PMR (which are uroflowmetry parameters) and BOO. We think that the Qmax value is one of the guiding parameters for assessing obstruction.

The accuracy of BWT measured by ultrasound in diagnosing BOO is noteworthy in this study and is consistent with findings from prior studies. However, no specific cut-off value for BWT is available. For the diagnosis of BOO, the cut-off point for BWT was 3.25 mm in Güzel et al. (19), 5 mm in Manieri et al. (20), 2 mm in Oelke et al. (21), and 2.9 mm in Kessler et al. (22). While BWT can be readily assessed using USG, its practical use as a diagnostic indicator for BOO is complex. BWT tends to be thin and is significantly impacted by the extent of bladder filling (21). In this study, USG was conducted at the point when patients reported feeling, their bladder was full. In our study, BOO was found to be 68.2% in patients with BWT >4 mm when the cut-off point was taken as 4 mm. In multivariate analyses, no correlation was found between BWT and BOO.

Unlike BWT, UEBW is not affected by bladder filling level (23). UEWB represents hypertrophy of the bladder wall and is thought to reflect BOO (24). Miyashita et al. (10), and Kojima et al. (24), reported the cut-off limit for UEBW as 35. Kojima et al. (24) reported that a higher UEBW significantly increased the risk of acute urinary retention. In our study, we evaluated the UEBW value as <35 and >35 in patients with BOO. The rate of BOO detection in patients with UEBW>35 was found to be 54.1%. In multivariate analyses, no correlation was found between UEBW and BOO.

IPP is a parameter measured by pelvic ultrasound that shows how much the prostate protrudes into the bladder. Enlargement of the prostate lobes causes BOO by narrowing the width of the bladder neck (25). IPP ≥10 mm for BOO increases the risk of acute urinary retention and decreases the response to medical treatment (26,27). Kuo et al. (28), reported that IPP had a positive predictive value of 72% for BOO. Chia et al. (29) associated the degree of IPP with BOO in their study. They graded the patients as IPP <5 mm, 5-10 mm, and >10 mm and investigated the severity of BOO according to their grades. While 94% of IPP Grade III patients had BOO, 79% of IPP Grade I patients had BOO on PFS. In our study, we divided our patients into three groups according to the degree of IPP. In patients with IPP >10 mm, the rate of BOO was 73.8%. In addition, in multivariate analyses, there was a statistically significant correlation between IPP and BOO. Our study showed that

Table 2. Univariate analysis of predicting factors for BOO

Parameters	BOO rate (%)	p-value
Age (year)		
50-59	22.6	
60-69	26.3	**0.003**
>70	51.8	
Maximal flow rate (mL/sec)		
<10	47.5	
10-15	23.1	**0.001**
>15	1.4	
Postvoid residual volume (mL)		
≥100	40.2	**0.006**
<100	27.3	
PSA (ng/dL)		
≥4	47.5	**0.001**
<4	28.4	
IPP (mm)		
<5	10.2	
5-10	29.4	**0.001**
>10	73.8	
UEBW (g)		
<35	20.1	**0.001**
≥35	54.8	
BWT (mm)		
<4	19.4	**0.001**
≥4	68.2	

BOO: Bladder outlet obstruction, BWT: Bladder wall thickness, UEBW: Ultrasound estimated bladder weight, IPP: Intravesical prostate protrusion

Table 3. Multivariate analysis of predictive factors for BOO

Variables	value	Adjusted odds ratio	95% CI	
			Lower	Upper
Maximal flow rate (mL/sec)	**0.001**	0.78	0.711	0.857
IPP (mm)	**0.001**	0.91	0.82	0.96

BOO: Bladder outlet obstruction, CI: Confidence Interval, IPP: Intravesical prostate protrusion

IPP can be used as a non-invasive parameter in patients with BOO.

Study Limitations

A noteworthy observation from the study findings is that all ultrasound-based morphological parameters, which exhibit high diagnostic precision in identifying BOO, can be conveniently assessed using suprapubic pelvic USG. The accessibility and non-invasive characteristics of this imaging modality render the evaluation of these anatomical factors suitable for regular clinical use. However, the current study is subject to certain limitations. Firstly, it did not investigate the impact of symptom duration and the severity of BOO. Secondly, only symptomatic patients were enrolled in the research. Consequently, the outcomes of the study may not be broadly applicable to individuals with asymptomatic BOO stemming from BPH.

CONCLUSION

The values of IPP and Qmax serve as significant non-invasive indicators for identifying BOO in individuals experiencing symptoms related to BPH. Clinicians can utilize these parameters in their clinical practice to aid in the diagnosis of BOO.

ETHICS

Ethics Committee Approval: This study was approved by University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital Non-interventional Research Ethics Committee (decision no: 2024/ 02-16, date: 04.03.2024).

Informed Consent: All clinical data were collected retrospectively from patients evaluated for LUTS between 2019-2023.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: Y.A., M.Z.K., Consept: Y.A., Design: Y.A., U.S., H.P., M.Z.K., Data Collection or Processing: Y.A., Analysis or Interpretation: Y.A., H.P., Literature Search: Y.A., M.Z.K., Writing: Y.A., U.S.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):221-224
DOI: 10.4274/BMJ.galenos.2025.2025.1-6

Case Report

High-Dose Radiation-Induced Bowel Perforation Leading to Thigh Necrotizing Fasciitis in a Cervical Cancer Case: A Case Report

Serviks Kanseri Olgusunda Yüksek Doz Radyasyona Bağlı Bağırsak Perforasyonun Neden Olduğu Uyluk Nekrotizan Fasiiti: Bir Olgu Sunumu

Vedat Öztürk[1], Mustafa Yalın[2]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Türkiye

[2]University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital, Clinic of Orthopedics and Traumatology, Elazığ, Türkiye

ABSTRACT

Necrotizing fasciitis is a rare, life-threatening soft tissue infection that is infrequently associated with sigmoid colon perforation, particularly following high-dose radiation therapy (RT) for cervical cancer. This case report presents a 58-year-old female patient with advanced cervical cancer treated with RT. She presented with general deterioration and left lumbar pain. Imaging studies revealed gas in the left hip and thigh, and extraluminal leakage suggestive of bowel perforation. Emergency laparotomy and surgical debridement confirmed a sigmoid colon perforation with stool contamination extending into the thigh. Despite aggressive interventions, including partial colon resection and fasciotomy, the patient succumbed to sepsis and multi-organ failure within 24 hours. This case highlights the rare but serious complication of necrotizing fasciitis secondary to radiation-induced sigmoid colon perforation, emphasizing the importance of early diagnosis and timely intervention.

Keywords: Radiation therapy, sigmoid perforation, necrotizing fasciitis

ÖZ

Nekrotizan fasiit, nadir görülen ve yaşamı tehdit eden bir yumuşak doku enfeksiyonudur. Özellikle serviks kanseri nedeniyle yüksek doz radyoterapi (RT) sonrası sigmoid kolon perforasyonu ile ilişkilendirilmesi oldukça nadirdir. Bu olgu sunumunda, ileri evre serviks kanseri nedeniyle RT uygulanan 58 yaşındaki bir kadın hasta ele alınmıştır. Hasta, genel durum bozukluğu ve sol lomber bölgede ağrı şikayetleriyle başvurmuş, görüntüleme çalışmaları sol kalça ve uylukta gaz varlığını ve bağırsak perforasyonunu düşündüren sızıntıyı ortaya koymuştur. Acil laparotomi ve cerrahi debridman sırasında sigmoid kolon perforasyonu ve dışkı kontaminasyonu doğrulanmıştır. Parsiyel kolon rezeksiyonu ve fasiotomi gibi agresif müdahalelere rağmen hasta, sepsis ve çoklu organ yetmezliği nedeniyle kaybedilmiştir. Bu olgu, radyasyon kaynaklı sigmoid kolon perforasyonuna bağlı nekrotizan fasiitin nadir ancak ciddi bir komplikasyonunu vurgulamaktadır ve erken tanı ile zamanında müdahalenin önemini göstermektedir.

Anahtar Kelimeler: Radyoterapi, sigmoid perforasyon, nekrotizan fasiit

INTRODUCTION

Necrotizing fasciitis is a rapidly progressive and often fatal soft tissue infection that involves the necrosis of subcutaneous tissues. It can be caused by various factors, with immunosuppression observed in only 0.2% of cases (1). Cervical cancer ranks as the second most frequent gynecological cancer in women worldwide. Radiation therapy (RT) has been widely used to treat cervical cancer over the past hundred years and remains the primary treatment option, especially for locally advanced disease (2). Sigmoid colon perforation is one of the most frequently reported complications of RT (3). There are case reports in the literature, describing thigh necrotizing fasciitis

Address for Correspondence: Vedat Öztürk MD, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Türkiye
E-mail: dr.ozturkvedat@gmail.com **ORCID ID:** orcid.org/0000-0003-2412-9725

Cite as: Öztürk V, Yalın M. High-dose radiation-induced bowel perforation leading to thigh necrotizing fasciitis in a cervical cancer case: a case report. Med J Bakirkoy. 2025;21(2):221-224

Received: 06.01.2025
Accepted: 15.04.2025
Publication Date: 04.06.2025

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associated with sigmoid colon perforation secondary to colon cancers and diverticulitis (4). However, to the best of our knowledge, there are no case reports of thigh necrotizing fasciitis secondary to sigmoid colon perforation resulting from high-dose RT for cervical cancer, making our case unique.

CASE REPORT

Informed consent for the case report was obtained from the patient's legal representatives.

A 58-year-old female patient presented to the emergency room with general malaise. She had no history of trauma but reported pain in the left lumbar region for approximately 45 days. A lumbar disc hernia had been diagnosed at another hospital, and physical therapy had been initiated. The patient reported that she had been unable to walk for the past 15 days due to pain and swelling in the left thigh, which had also prevented her from continuing physical therapy. Her general condition had deteriorated in recent days, leading to her admission to the emergency room.

Physical examination revealed tenderness in both lower quadrants of the abdomen, extensive edema, redness, and crepitation, upon palpation in the left lower extremity, extending to the ankle. Upon arrival, the patient's blood pressure was 80/50 mmHg, heart rate was 102/minute, temperature was 38.2 °C, and pulse oximetry was 92%. Laboratory results showed a white blood cell count of $8.56x10^9$/L, a creatinine 1.3 mg/dL, a hemoglobin 8 g/dL, a C-reactive protein 33 mg/dL, and a serum lactate 2.5 mmol/L.

Direct radiographs and computed tomography (CT) scans of the abdomen, pelvis, and lower extremities demonstrated the presence of gas in tissues consistent with necrotizing fasciitis, extending from the left iliac fossa, left hip, and left thigh down to the left ankle (Figure 1A-C). Coronal pelvic CT sections revealed abnormal air within the iliac fossa (Figure 1C). Contrast-enhanced CT in the sagittal plane showed the possible progression of a mass or abnormality originating in the iliac fossa, likely following the course of the iliopsoas muscle through the inguinal canal into the thigh compartments (Figure 1D). Additionally, axial CT sections showed widespread contrast material and a large air-fluid level within the iliac fossa (Figure 1E).

Considering necrotizing fasciitis of the left lower extremity secondary to bowel perforation, the patient underwent emergency surgery in collaboration with the general surgery team. Emergency laparotomy revealed that the sigmoid colon was adhering to the posterior abdominal wall and had perforated through this wall. An abscess was present in the retroperitoneum, and palpation of the thigh indicated stool drainage from the abdomen into the thigh. Following debridement, partial colon resection, and colostomy were performed. Fasciotomy was then performed with four incisions, on the medial and lateral sides of the thigh and leg. Extensive stool was found in the thigh (Figure 2A-B), reaching the knee and predominantly in the anterior compartment. Aggressive debridement was performed. Due to the patient's clinical deterioration, treatment, including inotropic support, was initiated in the intensive care unit. Unfortunately, the patient's lactic acidosis continued to worsen, and she died 24 hours later from sepsis and multi-organ failure.

DISCUSSION

Necrotizing fasciitis is a rapidly progressing and life-threatening infection that spreads along fascial planes in soft tissues (5). Early recognition of the disease and prompt initiation of emergency surgical debridement, along with broad-spectrum antibiotic therapy, can reduce mortality rates from 70% to 20% (6,7). Necrotizing fasciitis secondary to gastrointestinal tract perforation outside the perineum is very rare, it is often overlooked, diagnosed in the late stages, and generally has a fatal outcome (8).

RT uses high-energy beams or radioactive materials to target rapidly dividing cells with ionizing radiation. One of the most common complications of RT is radiation proctitis, which results from secondary damage to the rectal epithelium by ionizing radiation (9). Although RT does not directly cause necrotizing fasciitis, radiation applied to the abdominal area can cause epithelial damage to the bowel wall and lead to bowel perforations over time. These perforations, though rare, may result in the drainage of bowel contents into the peritoneal cavity, subsequently causing infection and necrotizing fasciitis in the affected extremity (10). Cases of thigh necrotizing fasciitis due to direct bowel perforations, independent of RT, have also been reported in the literature (8). In atypical presentations where other underlying causes are more prominent in the clinical history and the clinical features of necrotizing fasciitis are less apparent, diagnostic delays may occur, leading to increased morbidity and mortality.

Our case of thigh necrotizing fasciitis secondary to sigmoid colon perforation following high-dose RT for cervical cancer presents a rare but severe clinical scenario. This case, along with others described in the literature, demonstrates that necrotizing fasciitis can manifest with non-specific symptoms, leading to diagnostic delays. In this instance, the

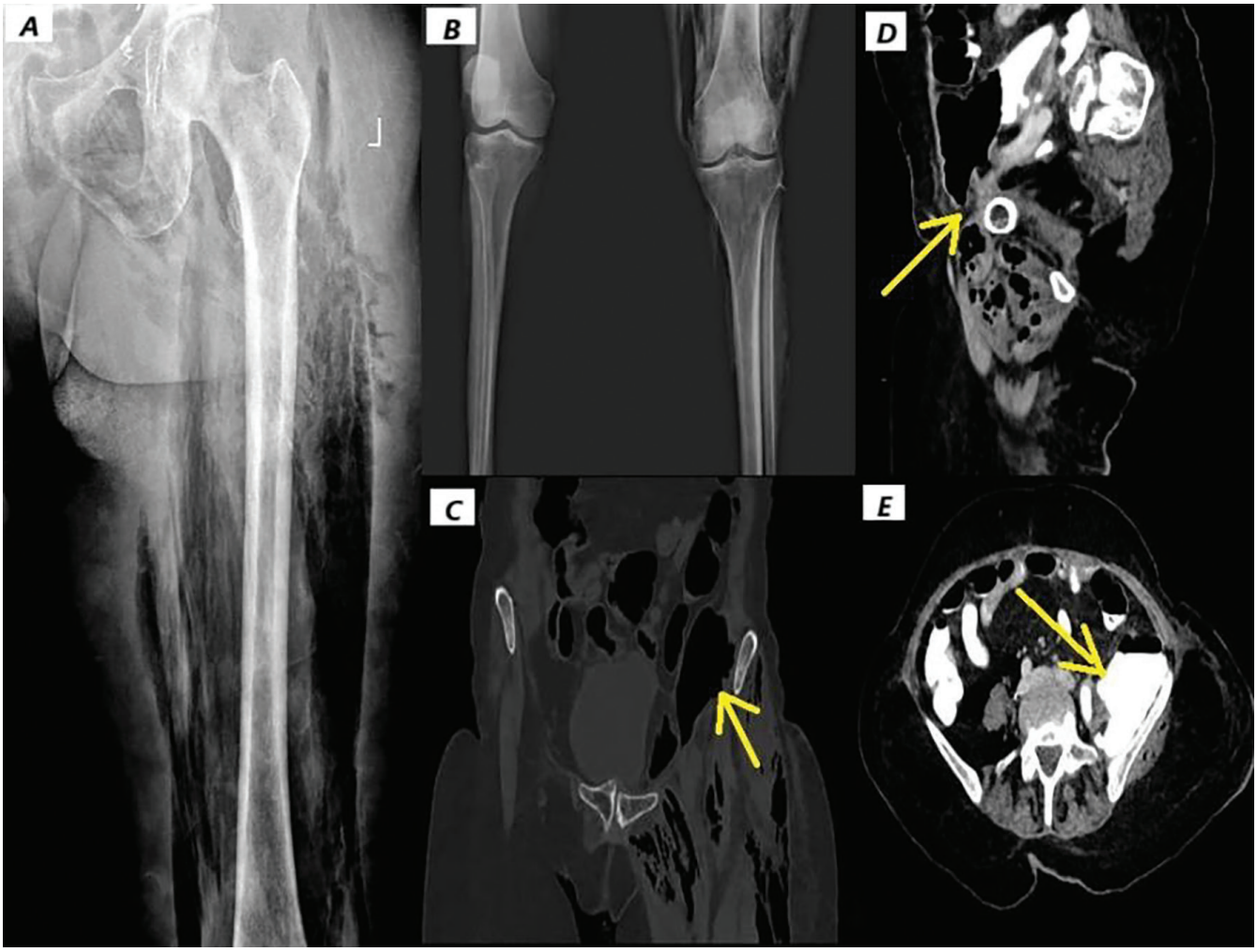


Figure 1. (A) A 58-year-old female patient anteroposterior pelvis and femur X-ray, abnormal gas pattern in the tissues overlying in the left hip and left thigh. (B) Abnormal gas pattern extended to the left cruris and ankle. (C) Abnormal gas pattern in the left iliac fossa on the coronal CT view. (D) The collection areas extended from the paravertebral area to the left inguinal canal on sagittal CT view. (E) Extralumination of the contrast agent into the iliac fossa on axial CT view

CT; Computed tomography

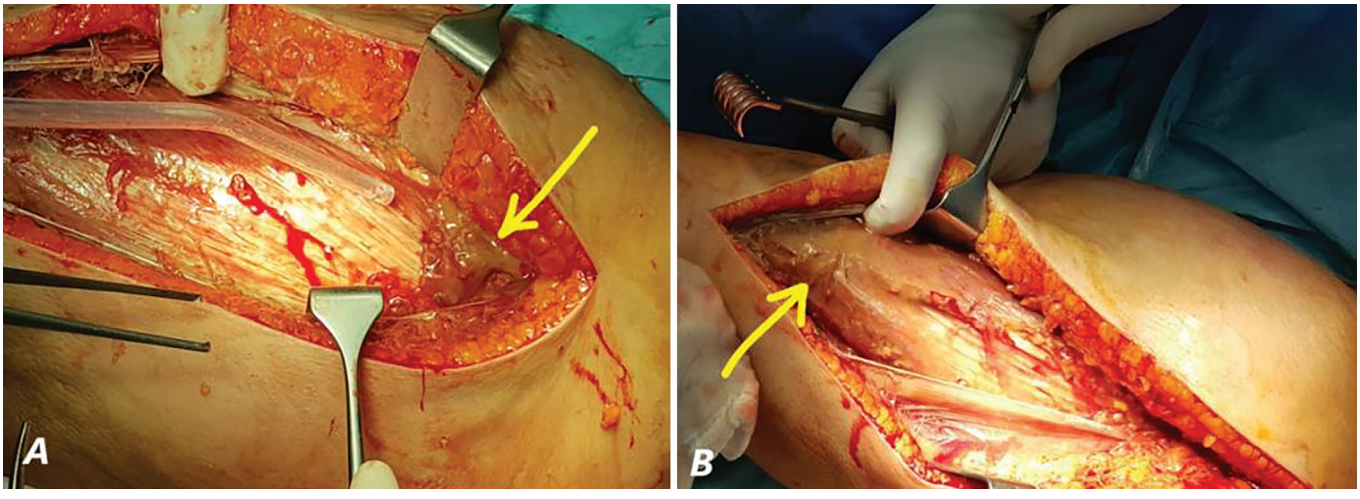


Figure 2. (A) Drainage of stool from the proximal area visualized after an extended lateral incision of the thigh. (B) Presence of stool draining down to the distal thigh and contaminating the thigh compartments

initial misdiagnosis of back pain as lumbar disc herniation, combined with the absence of any clinical history or findings related to bowel issues, delayed the recognition of bowel perforation and subsequent thigh necrotizing fasciitis. This delay contributed to the fatal progression of the disease.

These findings underscore the critical importance of maintaining a high index of suspicion for serious underlying causes in patients presenting with atypical or non-specific symptoms (11-13). Special caution is warranted in patients with a history of abdominal RT, as the long-term risk of bowel perforation and subsequent complications remains significant.

CONCLUSION

Aggressive surgical debridement remains the cornerstone of treatment for necrotizing fasciitis. Our case, along with others, highlights the necessity of timely surgical intervention to remove infected tissue and control the spread of infection (11,12). In cases where the infection spreads to the thigh through anatomical pathways, additional procedures such as colostomy may be required to manage fecal contamination and facilitate wound healing. Aggressive debridement is life-saving in necrotizing fasciitis. Subsequently, repeated debridements, negative pressure wound therapy, and in advanced cases, amputation may be effective in managing complex soft tissue infections and supporting recovery (11-15).

ETHICS

Informed Consent: Informed consent for the case report was obtained from the patient's legal representatives.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: V.Ö., M.Y., Consept: V.Ö., Design: M.Y., Data Collection or Processing: M.Y., Analysis or Interpretation: V.Ö., Literature Search: V.Ö., M.Y., Writing: V.Ö., M.Y.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: No fund was declared. No relevant financial activities outside the submitted work.

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