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RESEARCH ARTICLE

Magnetic resonance imaging assessment of the puborectalis muscle and anal sphincter in patients with anismus*

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ABSTRACT

Aim: This study aims to evaluate the significance of puborectalis muscle and anal sphincter thickness in the context of anismus.

Methods: We divided participants into three groups: patients with anismus (n=24), patients with pelvic floor dysfunction (PFD) (n=22), and a control group (n=24). On T2-weighted axial images, the thickness and circumference of both puborectalis muscles were measured at the level of the pubic symphysis, and the mean of these measurements was calculated. Additionally, the thicknesses of the external and internal anal sphincters were measured on T2-weighted axial magnetic resonance images at the level of the mid-anal canal, and the mean of these measurements was also calculated. Comparisons between groups were analyzed using ANOVA with post-hoc Tukey-HSD tests. ROC curve analysis was used to assess the diagnostic performance of key measurements, and interobserver agreement was evaluated using intraclass correlation coefficients (ICC).

Results: A total of 70 participants were included in the study, consisting of 24 patients with anismus (41.6% male), 22 patients with PFD (31.8% male), and 24 controls (45.8% male). Puborectalis muscle thicknesses were significantly higher in the anismus group compared to the PFD group, while the mean puborectalis thickness was significantly greater than that of the PFD group but not significantly different from controls. Additionally, the circumference of the puborectalis muscle was lower in the anismus group compared to the PFD group. ROC curve analysis indicated that puborectalis muscle thickness may potentially serve as a predictive marker for anismus, with an area under the curve of 0.667 (p=0.022). Good to excellent interobserver agreement was noted for the various measurements, with ICC values ranging from 0.762 to 0.970.

Conclusion: Our study suggests that puborectalis muscle and external anal sphincter measurements may aid in diagnosing anismus.

Keywords: Anismus, dyssynergic defecation, MR defecography, puborectalis muscle, sphincter

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INTRODUCTION

Anismus, also referred to as dyssynergic defecation, is a functional disorder characterized by obstructive symptoms and paradoxical contractions of the pelvic floor muscles (1). Anismus may develop due to the inability of the anal sphincter and/or puborectalis muscle to relax, or due to impaired abdominal and rectal pushing forces (2,3). Although innervated by different sources, the puborectalis muscle and external anal sphincter function as a unit (4). Patients with anismus often exhibit symptoms such as incomplete evacuation, the need for manual evacuation of stool, excessive straining, and prolonged evacuation time (5). Physiological tests such as manometry and electromyography are used for evaluating anismus; however, both false-positive and false-negative rates are high in manometry (1,3). In radiological evaluation, failure to observe the physiological 15-20° increase in the anorectal angle during defecation, prolonged evacuation time (greater than 30 seconds), and the presence of incomplete evacuation are assessed. The combination of these criteria allows for a radiological diagnosis of anismus (1,6-9). Magnetic resonance (MR) defecography also provides valuable information about accompanying pelvic floor abnormalities (2). However, there is no established reference standard for diagnosing anismus (3). Measuring static parameters, such as the thickness of the puborectalis muscle and anal sphincters at rest, may complement dynamic MR imaging by providing baseline structural insights that could refine the understanding of muscle abnormalities and their role in anismus pathophysiology.

The purpose of this study is to assess the role of the puborectalis muscle and anal sphincter thickness in anismus.

METHODS

This study protocol was approved by the Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (approval date:26.06.2024, number:154). Due to the retrospective design of the study, the requirement for written informed consent was waived. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (10).

Study design and participants

The anismus patient group was identified by searching MR defecography reports in the medical records of Bolu Abant İzzet Baysal University Training and Research Hospital from January 2014 to May 2024 using the keywords 'anismus' and 'dyssynergic defecation', resulting in the enrollment of 24 patients. A gender- and age-matched group of 22 patients with pelvic floor dysfunction (PFD) who had undergone MR defecography during the same period was also included. Additionally, 24 controls who underwent pelvic MR imaging for other reasons were recruited. Patients with inadequate imaging, a history of pelvic surgery or chemoradiotherapy, those under 18 years of age, and those with inflammatory bowel disease were excluded from the study.

Magnetic resonance imaging technique

MR images were obtained using a 1.5 Tesla MR imaging scanner (General Electric, Signa Explorer) with a phased-array body coil. After the instillation of 120-180 mL intrarectal sonographic gel in the decubitus position, sagittal, axial, and coronal T2-weighted images of the entire pelvis were acquired, along with mid-sagittal cine balanced/T2-weighted sequence images during squeezing, straining, and defecation, as recommended by the Society of Abdominal Radiology (7). The defecation phase was repeated at least three times to empty the rectum.

The routine pelvic MR protocol comprises sagittal, axial, and coronal T2-weighted images; axial T1-weighted images; diffusion-weighted images; and liver acquisition with volume acceleration (LAVA) sequences. Typical parameters of an axial T2 PROPELLER sequence include for MR defecography: TR 6000 ms, TE 120 ms, slice thickness/spacing of 4/1 mm, field of view 35 cm, acquisition matrix 320 × 320, and 4 excitations. For pelvic MR imaging: TR 4000 ms, TE 100 ms, slice thickness/spacing of 5/1 mm, field of view 32 cm, acquisition matrix 300 × 300, and 4 excitations.

Image interpretation

MR images were retrospectively evaluated by an experienced abdominal radiologist (ABY), and measurements were performed by two additional radiologists (AES, ST) who were blinded to the clinical data. On T2-weighted axial images, the thickness and circumference of both puborectalis muscles were measured at the level of the pubic symphysis, and the mean of these measurements was calculated (Figure 1). The thicknesses of the external and internal anal sphincters were measured on T2-weighted axial MR images at the level of the mid-anal canal, and the mean of these measurements was calculated (Figure 2).

Statistical analysis

Data analysis was conducted using the Statistical Package for the Social Sciences 24.0 software (IBM Corp., Armonk, NY, USA). Data distribution was assessed using the Shapiro-Wilk test. Descriptive statistics were reported as means with standard deviations for normally distributed variables and as medians with interquartile range (IQR) for others. Comparisons between the three groups were analyzed using one-way analysis of variance (ANOVA) test, followed by post-hoc test (Tukey-HSD). Since homogeneity of variances was violated, the Kruskal-Wallis test was used to compare right internal sphincter thickness and mean internal sphincter thickness. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of mean puborectalis muscle thickness, puborectalis muscle circumference, and mean external sphincter thickness to distinguish anismus. Interobserver agreement between the measurements of the two radiologists was quantified using the intraclass correlation coefficient (ICC). ICC values were classified as follows: less than 0.49 indicated poor reliability, values from 0.50 to 0.75

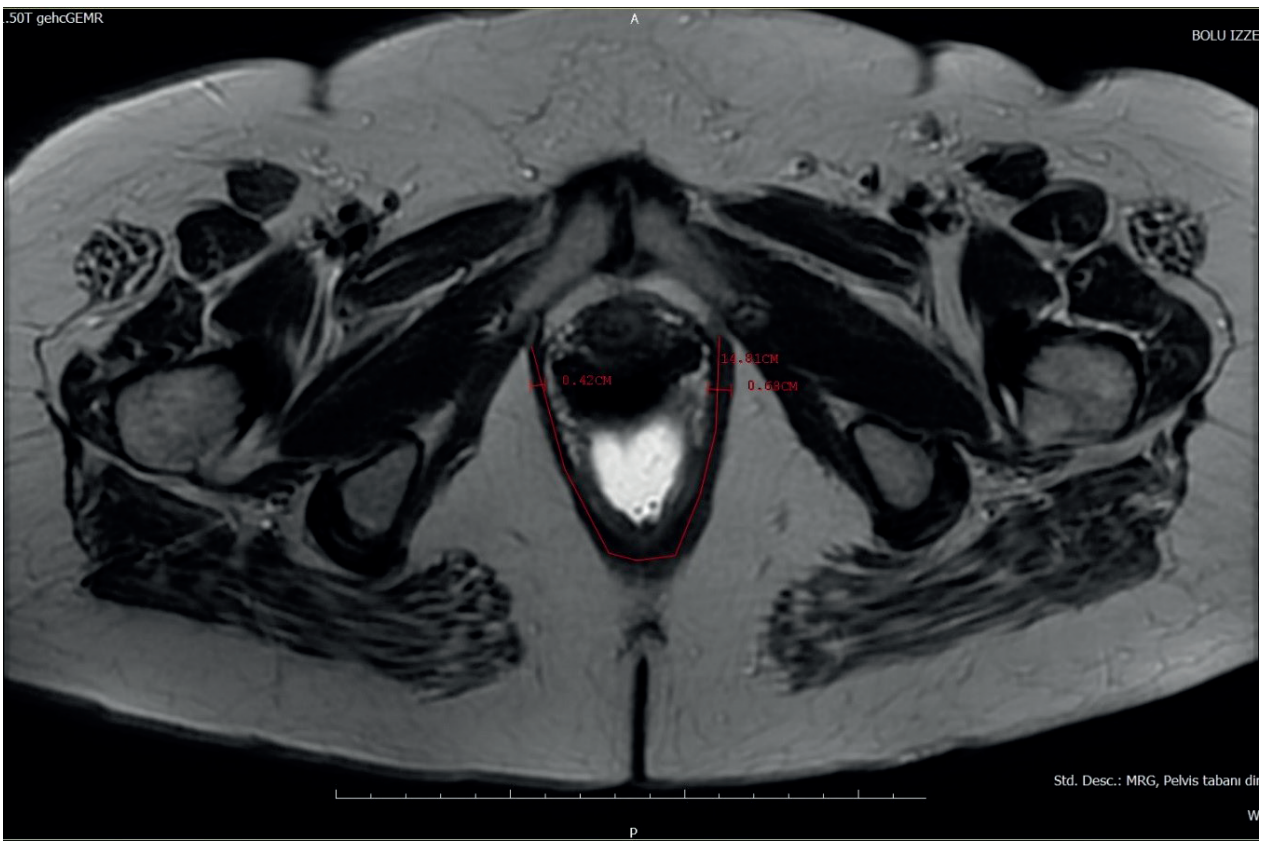

Figure 1. An example of measurements for puborectalis muscle thickness and circumference.

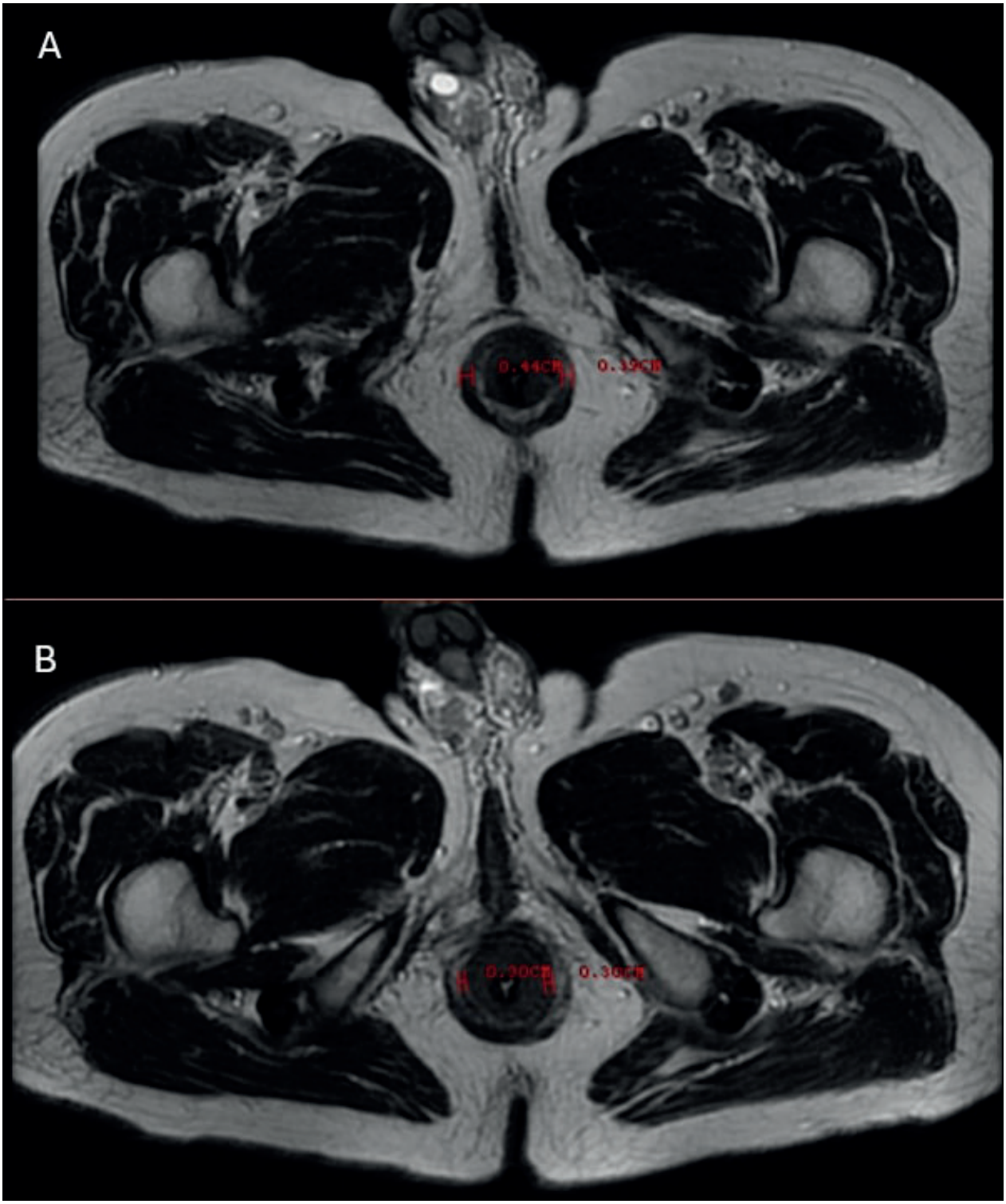

Figure 2. An example of measurements for external(A) and internal anal sphincter (B) thickness.

suggested moderate reliability, 0.75 to 0.89 reflected good reliability, and values between 0.90 and 1.00 indicated excellent reliability (11). The significance level was set to $p<0.05$ for all analyses.

RESULTS

The study included a total of 70 individuals, comprising 28 men and 42 women. The mean ages of the anismus, PFD, and control groups were 48.17 ± 13.8, 48.5 ± 14.4, and 48.21 ± 13.8 years, respectively, with no significant differences in mean age between the groups ($p=0.996$). The right puborectalis muscle thickness was significantly higher in the anismus group (6.04 ± 1.4 mm) compared to the PFD group (3.09 ± 1.3 mm, $p<0.0001$). However, it was significantly lower compared to the control group (7.04 ± 1.2 mm, $p=0.031$). The left puborectalis muscle thickness followed a similar pattern, as it was significantly higher in the anismus group (6.95 ± 1.7 mm) compared to the PFD group (3.23 ± 1.5 mm, $p<0.0001$), but not significantly different from the control group (7.17 ± 1.6 mm, $p=0.876$). The mean puborectalis muscle thickness in the anismus group (6.49 ± 1.5 mm) was significantly higher than in the PFD group (3.16 ± 1.3 mm, $p<0.0001$), but not significantly different from the control group (7.10 ± 1.3 mm, $p=0.274$). The puborectalis muscle circumference in the anismus group (104.90 ± 21.6 mm) was significantly lower than in the PFD group (126.55 ± 27.1 mm, $p=0.003$) but not significantly different from the control group (110.38 ± 14.5 mm, $p=0.654$).

Table 1. One-way analysis of variance (ANOVA) results

Parameter	Anismus group (n=24) Mean ± SD	Pelvic floor dysfunction group (n=22) Mean ± SD	Control group (n=24) Mean ± SD	Homogenity of variance test		One way ANOVA	
				Levene's statistic	p-value	F statistic	p-value
Age (years)	48.17 ± 13.8	48.5 ± 14.4	48.21 ± 13.8	0.107	0.899	0.004	0.996
Right puborectal muscle thickness (mm)	6.04 ± 1.4	3.09 ± 1.3	7.04 ± 1.2	0.580	0.563	53.817	<0.0001
Left puborectal muscle thickness (mm)	6.95 ± 1.7	3.23 ± 1.5	7.17 ± 1.6	0.026	0.974	43.651	<0.0001
Mean puborectal muscle thickness (mm)	6.49 ± 1.5	3.16 ± 1.3	7.10 ± 1.3	0.378	0.687	54.779	<0.0001
Puborectal mucle circumference (mm)	104.90 ± 21.6	126.55 ± 27.1	110.38 ± 14.5	2.627	0.080	6.211	0.003
Right internal sphincter thickness (mm)	1.76 ± 0.4	1,58 ± 0.2	1.78 ± 0.5	5.477	0.006*	1.999	0.144
Left internal sphincter thickness (mm)	1.75 ± 0.4	1.62 ± 0.4	1.73 ± 0.5	2.904	0.062	0.706	0.497
Mean internal sphincter thickness (mm)	1.76 ± 0.3	1.60 ± 0.3	1.75 ± 0.4	6.274	0.003*	1.482	0.235
Right external sphincter thickness (mm)	2.29 ± 0.6	2.46 ± 0.6	2.98 ± 0.8	1.249	0.293	6.716	0.002
Left external sphincter thickness (mm)	2.21 ± 0.5	2.28 ± 0.6	2.78 ± 0.8	3.059	0.054	4.477	0.015
Mean external sphinter thickness (mm)	2.25 ± 0.5	2.37 ± 0.6	2.84 ± 0.8	3.086	0.052	6.356	0.003

No statistically significant differences were detected among the three groups in terms of right, left, and mean internal anal sphincter thickness (p-values: 0.240, 0.497, and 0.235, respectively). Right and mean external sphincter thicknesses were statistically significantly lower in the anismus group (2.29 ± 0.6 mm and 2.25 ± 0.5 mm, respectively) compared to the control group (2.98 ± 0.8 mm, p=0.002; and 2.84 ± 0.8 mm, p=0.003, respectively). However, there were no statistically significant differences between the anismus group and the PFD group (p=0.685 and p=0.789, respectively). The number of cases participating in the study groups, their mean ages, and puborectalis muscle and anal sphincter thicknesses are summarized in Table 1 and Table 2.

Table 2. Post hoc test (Tukey HSD) results

Post-hoc test (Tukey HSD)				
	Group comparison	**Mean difference**	**p-value**	**95% Confidence interval (Lower and upper)**
Right puborectal muscle thickness (mm)	Anismus vs Control	-0.9958	0.031	-1.918 & -0.073
	Anismus vs Pelvic floor dysfunction	2.9508	<0.0001	2.008 & 3.894
	Control vs Pelvic floor dysfunction	3.9466	<0.0001	3.003 & 4.890
Left puborectal muscle thickness (mm)	Anismus vs Control	-0.2258	0.876	-1.328 & 0.876
	Anismus vs Pelvic floor dysfunction	3.7132	<0.0001	2.586 & 4.840
	Control vs Pelvic floor dysfunction	3.9390	<0.0001	2.812 & 5.066
Mean puborectal muscle thickness (mm)	Anismus vs Control	-0.61083	0.274	-1.5552 & 0.3335
	Anismus vs Pelvic floor dysfunction	3.33197	<0.0001	2.3664 & 4.2975
	Control vs Pelvic floor dysfunction	3.94280	<0.0001	2.9772 & 4.9084
Puborectal mucle circumference (mm)	Anismus vs Control	-5.4792	0.654	-20.373 & 9.414
	Anismus vs Pelvic floor dysfunction	-21.6504	0.003	-36.878 & -6.422
	Control vs Pelvic floor dysfunction	-16.1712	0.035	-31.399 & -0.943
Left internal sphincter thickness (mm)	Anismus vs Control	0.0208	0.983	-0.266 & 0.308
	Anismus vs Pelvic floor dysfunction	0.1360	0.511	-0.157 & 0.429
	Control vs Pelvic floor dysfunction	0.1152	0.617	-0.178 & 0.409
Right external sphincter thickness (mm)	Anismus vs Control	-0.6917	0.002	-1.163 & 0.221
	Anismus vs Pelvic floor dysfunction	-0.1671	0.685	-0.649 & 0.315
	Control vs Pelvic floor dysfunction	0.5246	0.03	0.043 & 1.006
Left external sphincter thickness (mm)	Anismus vs Control	-0.4958	0.019	-0.924 & -0.068
	Anismus vs Pelvic floor dysfunction	-0.0693	0.924	-0.507 & 0.369
	Control vs Pelvic floor dysfunction	0.4265	0.058	-0.012 & 0.865
Mean external sphincter thickness (mm)	Anismus vs Control	-0.5938	0.003	-1.012 & -0.173
	Anismus vs Pelvic floor dysfunction	-0.1182	0.789	-0.549 & 0.313
	Control vs Pelvic floor dysfunction	0.4756	0.027	0.045 & 0.906

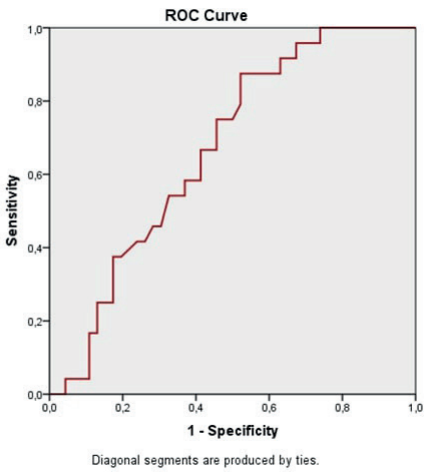

Figure 3. Receiver operating characteristic (ROC) curve analysis of the ability of puborectalis muscle thickness to predict anismus (area under the curve [AUC]: 0.667, cut-off value 6.125 mm with a sensitivity of 0.625 and specificity of 0.587).

Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the capacity of puborectalis muscle thickness to differentiate anismus. The analysis revealed that the area under the curve was 0.667, p-value was 0.022 (Figure 3). These findings highlight the potential of puborectalis muscle thickness as a predictive marker for anismus.

Good interobserver agreement was observed for measurements of the puborectalis muscle circumference, with an ICC value of 0.762. Excellent agreement was found for the thickness of the right and left puborectalis muscles, as well as for the mean internal and external sphincter thicknesses, with ICC values of 0.960, 0.938, 0.920, and 0.970, respectively.

DISCUSSION

In this retrospective comparative study, our primary objective was to investigate the relationship between puborectalis muscle and anal sphincter thickness and to evaluate their potential contribution to the MR defecography assessment of anismus. As we hypothesized, our results confirmed that puborectalis muscle thickness is significantly greater in patients with anismus compared to those with PFD, while not significantly different from that of healthy controls. These findings suggest that static measurements, particularly puborectalis muscle thickness, may serve as supportive imaging markers in the diagnosis of anismus, especially in cases where dynamic sequences are inconclusive or technically limited.

Anismus is considered a significant cause of chronic constipation; however, its diagnosis can be challenging due to the lack of specific findings and objective criteria (1-3,12). It is characterized by paradoxical contraction or failure of relaxation of the pelvic floor muscles (puborectalis muscle and external anal sphincter) during defecation (1). Though, in some cases, incomplete rectal evacuation results from low intrarectal pressure (2,3). Therefore, anismus encompasses a group of functional disorders with obstructive symptoms, and some authors prefer the term 'pelvic floor incoordination' instead of 'anismus' to broaden its scope (13).

The diagnosis of dyssynergic defecation is based on physiological and radiological tests, including digital rectal examination, anorectal manometry, electromyography, balloon expulsion test, evacuation proctography (X-ray defecography), MR defecography, and colonic transit studies (5). While anorectal manometry measures the pressure activity of anorectal muscles, balloon expulsion test helps estimate fecal transit time (14). The superiority of radiological methods over physiological tests is their ability to assess anatomical and structural problems (e.g., accompanying rectocele) at the same time (2,3). Conventional X-ray defecography provides valuable real-time information about the posterior compartment during defecation. However, due to radiation exposure and the need for contrast media, MR defecography has replaced X-ray defecography in modern practice (15). MR defecography enables the evaluation of all three pelvic compartments (14,15).

The major disadvantage of MR defecography is the non-physiological supine position during defecation (15). Static MR measurements may be helpful in cases where dynamic sequences are suboptimal or inconclusive. Specifically, static images can still provide important anatomical information that may support the diagnosis of anismus, such as the thickness and

symmetry of the puborectalis muscle, the anorectal angle at rest, and structural changes. These findings can complement dynamic imaging and offer additional diagnostic insight, especially in patients who are unable to perform adequate straining during dynamic sequences (16).

In this study, we hypothesized that there is a positive correlation between the thickness of the puborectalis muscle and the thickness of the external anal sphincter in patients with anismus. Previous studies are primarily focused on dynamic anorectal angle measurement, M-line measurement (distance between pubococcygeal line and anorectal junction), anal canal length measurement, sphincteric thickness measurement, and rectal emptying ratios (2,3). Few studies have investigated the relationship between the puborectalis muscle and anismus (17,18).

A recent study conducted by Çamur et al. identified cut-off values for puborectalis muscle thickness and abdominal subcutaneous adipose tissue thickness in diagnosing anismus (17). Our study demonstrated significant differences in puborectalis muscle thickness and circumference, as well as external anal sphincter thickness, among the three groups. In their study, the cut-off value for mean puborectalis muscle thickness was slightly lower than our results (17). These findings support the role of the puborectalis muscle and external anal sphincter in functional disorders. The high interobserver agreement in our measurements indicates that MR defecography is a reliable method for evaluating anismus and PFD.

Another study conducted by Chu et al. reported that children with anismus exhibit a smaller anorectal angle and paradoxical contraction of the puborectalis muscle. However, it is not yet fully understood whether these findings are due to the pathophysiology of the condition or its consequences (18). Paradoxical puborectalis muscle contraction is a form of chronic constipation and is associated with prolonged and repeated straining, as well as incomplete evacuation of the rectum (19,20). A deep impression of the puborectalis sling on the posterior rectal wall at rest, as seen on MR defecography, has been identified as a finding indicative of paradoxical puborectalis muscle contraction (21). An important point to keep in mind is that paradoxical sphincter contraction during digital rectal examination or anorectal manometry can also occur in healthy individuals, potentially leading to the overdiagnosis of anismus (21,22).

In the article published by Haliloğlu et al. in 2022, patients with anismus and perineal descent were compared, and no significant differences were found in the thickness of the internal and external anal sphincters (2). In our study, while no significant differences were observed in internal sphincter thickness, the mean external sphincter thickness was found to be higher in the control group compared to the anismus and PFD groups, with no notable difference between the anismus and PFD groups. The internal anal sphincter thickness values in our study were abnormally low across all groups, in clear contrast to the values commonly observed and reported in clinical practice worldwide, which typically range from 4.9 to 5.5 mm (23). The choice of axial imaging plane may have influenced our interpretation, and caused this discrepancy. Future studies may benefit from utilizing oblique planes perpendicular to the anal canal's long axis to enhance the accuracy of sphincter thickness measurements and minimize the risk of anatomical misidentification.

The main limitation of this study is that the patient diagnoses were not confirmed through anorectal manometry or balloon expulsion testing but were based solely on clinical and radiological data. The retrospective design and the small sample size also represent notable limitations. The lack of data on parity and menopausal status, both of which may influence pelvic floor muscle morphology, is an additional constraint. Due to the retrospective design of the study and incomplete clinical documentation, we were unable to control for or analyze the potential effects of these variables.

Since there are no specific findings to establish a diagnosis of anismus in MR defecography, diagnosing anismus can be challenging. In non-cooperative patients, MR defecography findings may be confused with anismus. Our study suggests that changes in puborectalis muscle thickness and circumference, as well as external anal sphincter thickness, may provide important insights for diagnosing anismus and PFD.

Ethical approval

This study has been approved by the Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (approval date 26/06/2024, number 154). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: ABY, AES, ST; Concept: ABY, AES, ST; Design: ABY, AES, ST; Data Collection or Processing: ABY, AES, ST; Analysis or Interpretation: ABY, AES, ST; Literature Search: ABY, AES, ST; Writing: ABY, AES, ST. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Pisano U, Irvine L, Szczachor J, Jawad A, MacLeod A, Lim M. Anismus, physiology, radiology: is it time for some pragmatism? A comparative study of radiological and anorectal physiology findings in patients with anismus. Ann Coloproctol. 2016; 32(5): 170-4. **[Crossref]**
2. Haliloğlu N, Arslan MF, Erden A. Comparison of anismus and perineal descent on static images of magnetic resonance defecography: can we rule out anismus in patients who can not defecate? Turk J Colorectal Dis. 2022; 32: 54-8. **[Crossref]**
3. Öz DK, Haliloğlu N, Erden A. MR defecography findings suggesting anismus: reliable or not reliable? Journal of Ankara University Faculty of Medicine. 2022; 75(4): 515-9. **[Crossref]**
4. Andromanakos N, Filippou D, Karandreas N, Kostakis A. Puborectalis muscle and external anal sphincter: a functional unit? Turk J Gastroenterol. 2020; 31(4): 342-3. **[Crossref]**
5. Rao SS, Patcharatrakul T. Diagnosis and treatment of dyssynergic defecation. J Neurogastroenterol Motil. 2016; 22(3): 423-35. **[Crossref]**
6. Reiner CS, Tutuian R, Solopova AE, Pohl D, Marincek B, Weishaupt D. MR defecography in patients with dyssynergic defecation: spectrum of imaging findings and diagnostic value. Br J Radiol. 2011; 84(998): 136-44. **[Crossref]**
7. Lalwani N, Khatri G, El Sayed RF, et al. MR defecography technique: recommendations of the society of abdominal radiology's disease-focused panel on pelvic floor imaging. Abdom Radiol (NY). 2021; 46(4): 1351-61. **[Crossref]**
8. Halligan S, Malouf A, Bartram CI, Marshall M, Hollings N, Kamm MA. Predictive value of impaired evacuation at proctography in diagnosing anismus. AJR Am J Roentgenol. 2001; 177(3): 633-6. **[Crossref]**
9. Roberts JP, Womack NR, Hallan RI, Thorpe AC, Williams NS. Evidence from dynamic integrated proctography to redefine anismus. Br J Surg. 1992; 79(11): 1213-5. **[Crossref]**
10. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg. 2014; 12(12): 1495-9. **[Crossref]**
11. Koo TK, Li MY. A Guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med. 2016; 15(2): 155-63. **[Crossref]**
12. Lee KH, Kim JY. Current situation on the diagnosis of anismus-discordances between imaging and a physiologic study. Ann Coloproctol. 2016; 32(5): 159. **[Crossref]**
13. van Dam JH, Schouten WR, Ginai AZ, Huisman WM, Hop WC. The impact of anismus on the clinical outcome of rectocele repair. Int J Colorectal Dis. 1996; 11(5): 238-42. **[Crossref]**
14. Sadeghi A, Akbarpour E, Majidirad F, et al. Dyssynergic defecation: a comprehensive review on diagnosis and management. Turk J Gastroenterol. 2023; 34(3): 182-95. **[Crossref]**
15. Nijland DM, van Genugten LT, Dekker KS, et al. The added value of conventional defecography and MRI defecography in clinical decision making on treatment for posterior compartment prolapse. Int Urogynecol J. 2023; 34(2): 507-15. **[Crossref]**
16. Davra SV, Jain A, Kumar A. Static & dynamic pelvic floor assessment using MR defecography: a radiological prospective observational study with ideal reporting template. Egypt J Radiol Nucl Med. 2025; 56: 34. **[Crossref]**
17. Çamur E, Acar D. Can puborectalis muscle and abdominal subcutaneous adipose tissue thickness indicate dyssynergic defecation? New Trends in Medicine Sciences. 2024; 5(3): 168-73. **[Crossref]**

18. Chu WC, Tam YH, Lam WW, Ng AW, Sit F, Yeung CK. Dynamic MR assessment of the anorectal angle and puborectalis muscle in pediatric patients with anismus: technique and feasibility. J Magn Reson Imaging. 2007; 25(5): 1067-72. **[Crossref]**

19. Landmann RG, Wexner SD. Paradoxical puborectalis contraction and increased perineal descent. Clin Colon Rectal Surg. 2008; 21(2): 138-45. **[Crossref]**

20. Payne I, Grimm LM. Functional disorders of constipation: paradoxical puborectalis contraction and increased perineal descent. Clin Colon Rectal Surg. 2017; 30(1): 22-9. **[Crossref]**

21. Kim AY. How to interpret a functional or motility test - defecography. J Neurogastroenterol Motil. 2011; 17(4): 416-20. **[Crossref]**

22. Harmston C. Anismus. In: Lindsey I, Nugent K, Dixon T, editors. Pelvic floor disorders for the colorectal surgeon. Oxford; 2010. **[Crossref]**

23. Huebner M, Margulies RU, Fenner DE, Ashton-Miller JA, Bitar KN, DeLancey JO. Age effects on internal anal sphincter thickness and diameter in nulliparous females. Dis Colon Rectum. 2007; 50(9): 1405-11. **[Crossref]**

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RESEARCH ARTICLE

The role of serum amyloid A as an inflammatory biomarker in patients with chronic inflammatory conditions

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ABSTRACT

Aim: This study aimed to evaluate the diagnostic value of serum amyloid A (SAA) by comparing it with conventional acute phase markers (APMs), such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fibrinogen, in patients experiencing pain related to chronic inflammatory and gallbladder diseases.

Materials and Methods: We retrospectively examined data retrieved from the medical records of 601 patients diagnosed with chronic inflammatory disease, gallbladder stones who underwent cholecystectomy between January 2020 and June 2023. We compared serum levels of ESR, SAA, CRP, and fibrinogen during episodes of pain.

Results: The study population consisted of 601 patients, of whom 401 (66.72%) were female and 200 (33.28%) were male. The mean age was 48.74±17.20 years for females and 46.62±17.52 years for males. Serum SAA, CRP, ESR, and fibrinogen levels showed a statistically significant positive correlation. The most significant correlation was between SAA and CRP. However, there was no rise in CRP or other acute phase markers (APMs), even though SAA rose in about one-fourth of the patients (24.7%).

Conclusion: Monitoring chronic inflammatory diseases with SAA is thought to be useful for detecting subclinical inflammation and underlying chronic inflammatory diseases. It may also prevent the development of amyloidosis and therefore morbidity and mortality.

Keywords: Chronic inflammatory diseases, serum amyloid A, C-reactive protein, erythrocyte sedimentation rate, fibrinogen

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INTRODUCTION

Acute phase markers (APMs) are biomarkers that show significant changes in serum concentration when inflammation is present. The most common APMs used in clinical practice are C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid A (SAA), and fibrinogen (1,2).

Persistent inflammation, resulting from prolonged exposure to stimulation or an inappropriate immune reaction against self-molecules, can progress to the chronic phase, in which tissue damage and fibrosis take place. Chronic inflammation may contribute to numerous diseases, including arthritis, atherosclerosis, autoimmune diseases, and age-related conditions (3).

The acute phase protein SAA plays an important role in acute and chronic inflammation (4). SAA amyloidosis, also known as secondary amyloidosis, is a known consequence of chronic inflammation (5). Patients with Familial Mediterranean fever (FMF) have been the focus of the most comprehensive studies on SAA. In patients with FMF, SAA levels are increased not only during attacks but also during attack-free periods. These attack-free periods have been shown to result in persistent subclinical inflammation and, eventually, amyloidosis (6,7).

Gallstone disease affects approximately one-fifth of the world's population (between 15% and 25%) (8). One cause of stone and sludge formation in the gallbladder is amyloid deposition due to increased level of SAA protein. There are few case reports about amyloid deposition in the gallbladder or biliary tract (9,10). However, these reports do not refer to SAA levels.

The aim of this study was to compare serum levels of SAA with those of CRP, ESR, and fibrinogen in patients with gallbladder stone disease without acute cholecystitis, patients suffering from persistent abdominal and back pain after cholecystectomy, and patients with chronic inflammatory diseases.

MATERIALS AND METHODS

Subjects

This single-center study was conducted by retrospectively scanning the files of admitted patients from the hospital database of Lokman Hekim University Ankara Hospital, covering the period between January 2020 and June 2023. The study was approved by the scientific research ethics committee of Lokman Hekim University (Date: 03/06/2023 Number: 2023/88). Due to the retrospective nature of the study, obtaining informed consent from patients was waived. This study was conducted in accordance with the ethical principles defined in the Declaration of Helsinki. No artificial intelligence was used in preparing this article for publication.

The patients included in the study were those whose symptoms persisted despite treatment with nonsteroidal anti-inflammatory drugs, glucocorticoids, or other medications for their diagnosed conditions. Those who met the study's requirements were at least 18 years old, and had a confirmed diagnosis of one of the following: FMF, rheumatoid arthritis (RA), seronegative arthritis (SnA), psoriatic arthritis (PA), inflammatory bowel disease (IBD) (ulcerative colitis or Crohn's disease), gallstones without acute cholecystitis; or had undergone a cholecystectomy due to gallstones, and had abdominal, back, or joint pain that had lasted for at least six months despite ongoing treatment. ESR, SAA, CRP, and fibrinogen levels were measured during episodes of pain. The study excluded individuals under the age of 18, those without a definitive diagnosis, and whose SAA, ESR, CRP, and fibrinogen levels were not measured during the pain episodes.

Laboratory analysis

SAA levels were measured using the nephelometric method with the Snibe Maglumi 2000 device (Shenzhen New Industries Biomedical Engineering Co., Ltd., China), with a normal value of <0.3 mg/dL (11). Fibrinogen levels were measured by the photooptic

method using a Sigma Diagnostics Amelung AMAX 200 analyzer (Sigma-Aldrich Co., Inc., Germany), with a reference range of <400 mg/dL (12). CRP was measured by the turbidimetric method with a Cobas C501 Chemistry Analyzer (Roche Diagnostics GmbH, Mannheim, Germany), with a normal value of <5 mg/L (13). ESR was measured by the Westergren method (mm/h).

Statistical analysis

All data were evaluated using SPSS statistical software for Windows (version 26, SPSS, Armonk, NY, USA). Descriptive statistics were presented as n (%), minimum-maximum values, mean, and % standard deviation. Normality of distribution was assessed using the Kolmogorov–Smirnov test for all variables. Since the data did not fit into the normal distribution, correlation analysis was performed using the Spearman correlation test to evaluate the relationships between SAA, CRP, ESR, and fibrinogen. A P value of <0.05 was considered statistically significant.

RESULTS

The study population consisted of 601 patients, including 401 females (66.72%) and 200 males (33.28%). Age was between 18-90, mean ± SD: 48.74±17.20 years in females, and between 18-88, mean ± SD: 46.62±17.52 years in males. Out of the 601 patients, 143 (23.79%) had seronegative arthritis, 109 (18.14%) had RA, 23 (3.83%) had psoriatic arthritis, 123 (20.46%) had FMF, 120 (19.97%) had inflammatory bowel disease, 54 (8.98%) had undergone cholecystectomy, and 29 (4.83%) had gallstones (Table 1).

Serum concentrations of fibrinogen, CRP, ESR, and SAA assessed during pain episodes were compared. Fibrinogen levels ranged from 28 to 853 mg/dL (mean ± SD: 328.81± 90.90), CRP levels ranged from 0.18 to 280 mg/L (mean ± SD: 25.86±49.85), ESR levels ranged from 2-140 mm/h (mean ± SD: 25.34 ± 23.7), and SAA levels ranged from 0 to 135 mg/dL (mean ±

Table 1. Demographic, clinical, and laboratory characteristics of patients

Age (Year)	48.64 ± 17.47 (16-90)
Gender	
Female	401 (66.72)
Male	200 (33.27)
Diagnosis	
Rheumatoid arthritis	109 (18.13)
Psoriatic arthritis	23 (3.82)
Familial Mediterranean Fever	123 (20.46)
Seronegative arthritis	143 (23.67)
Inflammatory bowel disease	120 (19.96)
Gallstones	29 (4.82)
Cholecystectomy	54 (8.98)
Laboratory	
SAA (n=601)	6.29 ± 11.86 (0.00 - 135.00)
CRP (n=401)	25.86 ± 49.85 (0.18 - 280.00)
ESR (n=172)	25.34 ± 23.97 (2.00 - 140.00)
Fibrinogen (n=419)	328.81 ± 90.90 (28.00 - 853.00)

SAA: Serum Amyloid A (mg/dL), CRP: C-Reactive Protein (mg/L), ESR: Erythrocyte Sedimentation Rate (mm/hour), Fibrinogen (mg/dL).

Category data is presented in the form of n (%).

Metric data is presented in the form of mean ± standard deviation (min-max).

Table 2. Laboratory Values of Patients

	n	%	Minimum	Maximum	Mean	% SD
SAA (Total)	601	100	0.00	135.00	6.29	11.86
Female	401	66.7	0.00	135	5.36	11.90
Male	200	33.3	0.01	51.80	8.15	11.59
CRP (Total)	401	66.7	0.18	280.00	25.86	49.85
Female	270	67.4	0.19	235	22.19	43.84
Male	131	32.6	0.18	280	33.44	59.85
ESR (Total)	172	28.6	2.00	140	25.34	23.97
Female	122	70.6	4	140	27.81	24.46
Male	50	29.4	2	122	19.49	21.91
Fibrinogen (Total)	419	69.4	28.00	853.00	328.81	90.90
Female	293	69.9	28.00	853.00	326.60	92.94
Male	126	30.1	171.00	746.00	333.95	86.11

SD: Standard Deviation, SAA: Serum Amyloid A (mg/dL), CRP: C-Reactive Protein (mg/L), ESR: Erythrocyte Sedimentation Rate (mm/hour), Fibrinogen (mg/dL).

Table 3. Correlation between SAA and other APMs

	r	p
CRP	0.774	<0.001
ESR	0.533	<0.001
Fibrinogen	0.518	<0.001

SAA: Serum Amyloid A (mg/dL), APM: Acute Phase Marker, CRP: C-Reactive Protein (mg/L), ESR: Erythrocyte Sedimentation Rate (mm/hour), Fibrinogen (mg/dL).

SD: 6.29±11.86). Even though SAA increased, there was no rise in CRP or other APMs in about a quarter of the patients (24.7%) (Table 2).

The levels of serum fibrinogen, CRP, ESR, and SAA exhibited a statistically significant positive correlation ($p<0.001$). SAA and CRP showed the strongest correlation (Spearman's rho: 0.77) (Table 3).

DISCUSSION

CRP is the most commonly used APM. However, CRP does not always increase during acute inflammation, whereas SAA often does. In fact, it is common to find elevated SAA levels while CRP or other APMs remain within normal limits, but it is rare for CRP or other APMs to increase without a rise in SAA. Additionally, in cases of mild chronic inflammation, SAA can remain elevated even when CRP is within the normal range (14-16).

While some studies suggest that CRP could substitute for SAA, especially in the follow-up of FMF, it is clear that CRP alone is not sufficient. A study by Duzova et al. confirmed that SAA is the most reliable marker for monitoring inflammation in FMF patients during attack-free periods (17). Similarly, in a study, Sözel et al. reported that SAA is the best marker during attack-free periods in FMF, but CRP can be used as an alternative in cases where SAA levels cannot be measured (18). SAA levels, which are considered to be related to amyloidosis, were reported to be high in nearly 30% of cases during inter-episode periods (19).

In the present study, 24.7% of patients exhibited increased SAA levels, while CRP and other APMs remained within normal limits. This suggests that although CRP is generally considered a reliable indicator of inflammation, approximately one-quarter of patients still experience inflammation without a corresponding rise in CRP. Therefore, SAA appears to be a superior marker for detecting persistent inflammation compared to traditional APMs.

This study is also unique in that it includes patients with gallbladder diseases to assess chronic inflammation. These patients were compared with those suffering from other chronic inflammatory diseases. This comparison is important because amyloid deposits have been detected in the gallbladder and bile ducts in some cases (9,10). The patients in these cases also face a long-term risk of developing amyloidosis.

Amyloidosis is a serious cause of morbidity and mortality, affecting organs such as the kidneys, heart, gallbladder, and biliary tract. Monitoring ongoing inflammation in patients with chronic conditions is crucial to prevent complications such as renal failure and cardiovascular disease caused by amyloidosis. This benefits both the patients and the healthcare system.

The reason for including symptomatic gallbladder diseases in this study is that, similar to other chronic inflammatory diseases where complaints continue despite treatment, symptoms may persist due to chronic inflammation in gallbladder diseases. Another reason is the possibility of undiagnosed FMF in patients with symptomatic gallbladder disease and other chronic inflammatory conditions.

In patients experiencing abdominal and back pain attacks, if such attacks recur post-cholecystectomy and acute phase reactants remain elevated, FMF could be considered as the underlying cause. In instances where referred back pain due to gallstones is under consideration, postoperative back pain may be attributable to FMF-related sacroiliitis.

Although it has not been conclusively proven that the persistent abdominal and back pain seen in patients with gallstones or post-cholecystectomy is linked to elevated SAA levels and amyloid deposits in the gallbladder or biliary tract, this study provides a foundation for future research on this topic.

Measuring SAA levels during pain episodes in chronic inflammatory diseases is considered to be a reliable chronic phase marker, in addition to being a better APM than CRP, since it also shows ongoing mild chronic inflammation. Although SAA testing is more expensive than CRP when considered individually, it has been shown to be more economically beneficial in the long term. This is due to its ability to detect chronic inflammation, facilitate the early diagnosis of undiagnosed FMF cases, and help prevent the development of amyloidosis, thereby reducing the associated morbidity and mortality. Furthermore, providing symptomatic pain relief with colchicine for patients who experience persistent pain after cholecystectomy will increase patient comfort and reduce pain-related visits to health institutions.

This study has a retrospective design, which limits the ability to control for confounding factors and ensure consistency in treatment protocols, medication adherence, and symptom documentation over time. Pain assessment was based on clinical records without standardized scales or structured follow-up intervals, which may have introduced subjectivity or inconsistencies in symptom classification. Although increased SAA levels may suggest ongoing inflammation or potential amyloid deposition, no histopathological confirmation of amyloidosis was obtained in patients with persistent symptoms after cholecystectomy. SAA levels were measured only once during a painful episode, so they may not fully reflect the dynamic inflammatory profile or its progression over time.

Future prospective studies incorporating serial SAA measurements, standardized pain assessment tools, and histopathological examination of tissues may help confirm the clinical value of SAA in the diagnosis and management of chronic inflammation and assessing the risk of amyloidosis.

CONCLUSION

The findings of this study suggest that monitoring SAA levels may be more useful than monitoring other conventional APMs, particularly during painful periods, for patients with chronic inflammatory and gallbladder diseases. Monitoring chronic inflammatory diseases with SAA has proven to be a useful tool for detecting subclinical inflammation, identifying underlying chronic inflammatory diseases, and preventing the development of amyloidosis and its associated morbidity and mortality.

Ethical approval

This study has been approved by the Lokman Hekim University Scientific Research Ethics Committee (approval date 03/06/2023, number 2023/88).

Author contribution

Concept: AOA; Design: AOA; Data Collection or Processing: AOA; Analysis or Interpretation: AOA; Literature Search: AOA; Writing: AOA. The author reviewed the results and approved the final version of the article.

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Conflict of interest

The author declare that there is no conflict of interest.

REFERENCES

1. Gulhar R, Ashraf MA, Jialal I. Physiology, Acute Phase Reactants. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
2. Mantovani A, Garlanda C. Humoral Innate Immunity and Acute-Phase Proteins. N Engl J Med. 2023; 388(5): 439-52. [Crossref]
3. Germolec DR, Shipkowski KA, Frawley RP, Evans E. Markers of Inflammation. Methods Mol Biol. 2018; 1803: 57-79. [Crossref]
4. Zhang Y, Zhang J, Sheng H, Li H, Wang R. Acute phase reactant serum amyloid A in inflammation and other diseases. Adv Clin Chem. 2019; 90: 25-80. [Crossref]
5. Thorne J, Clark D, Geldenhuys L, More K, Vinson A, Tennankore K. Serum Amyloid A Protein-Associated Kidney Disease: Presentation, Diagnosis, and Management. Kidney Med. 2022; 4(8): 100504. [Crossref]
6. Sack GH. Serum amyloid A - a review. Mol Med. 2018; 24(1): 46. [Crossref]
7. Çakan M, Karadağ ŞG, Tanatar A, Sönmez HE, Ayaz NA. The Value of Serum Amyloid A Levels in Familial Mediterranean Fever to Identify Occult Inflammation During Asymptomatic Periods. J Clin Rheumatol. 2021; 27(1): 1-4. [Crossref]
8. Gutt C, Schläfer S, Lammert F. The Treatment of Gallstone Disease. Dtsch Arztebl Int. 2020; 117(9): 148-58. [Crossref]
9. Matsuda S, Nishikata M, Takai K, et al. An Unusual Case of Acute Cholecystitis with Amyloidosis: A Case Report and Literature Review. Intern Med. 2019; 58(6): 803-7. [Crossref]
10. Kwon AH, Tsuji K, Yamada H, Okazaki K, Sakaida N. Amyloidosis of the gallbladder mimicking gallbladder cancer. J Gastroenterol. 2007; 42(3): 261-4. [Crossref]
11. Sack GH Jr. Serum amyloid A - a review. Mol Med. 2018; 24(1): 46. [Crossref]
12. Dobson DA, Fish RJ, de Vries PS, Morrison AC, Neerman-Arbez M, Wolberg AS. Regulation of fibrinogen synthesis. Thromb Res. 2024; 242: 109134. [Crossref]
13. Pathak A, Agrawal A. Evolution of C-Reactive Protein. Front Immunol. 2019; 10: 943. [Crossref]
14. Sorić Hosman I, Kos I, Lamot L. Serum Amyloid A in Inflammatory Rheumatic Diseases: A Compendious Review of a Renowned Biomarker. Front Immunol. 2021; 11: 631299. [Crossref]
15. Hwang YG, Balasubramani GK, Metes ID, Levesque MC, Bridges SL, Moreland LW. Differential response of serum amyloid A to different therapies in early rheumatoid arthritis and its potential value as a disease activity biomarker. Arthritis Res Ther. 2016; 18(1): 108. [Crossref]
16. Hu QL, Fu S, Huang R, Zhang L, Wu LF, Lv YJ. The Value of Serum Amyloid A in the Diagnosis and Management of Ankylosing Spondylitis. Int J Gen Med. 2021; 14: 2715-9. [Crossref]
17. Duzova A, Bakkaloglu A, Besbas N, et al. Role of A-SAA in monitoring subclinical inflammation and in colchicine dosage in familial Mediterranean fever. Clin Exp Rheumatol. 2003; 21(4): 509-14.
18. Sözel H, Yılmaz F, Avşar E, Maştaoğlu E, Alemdar MS, Bora F. Erişkin Ailevi Akdeniz Ateşi Hastalarında Ataksız Dönemdeki Serum Amiloid A'nın Diğer İnflamatuar Belirteçlerle Korelasyonu. Osmangazi Tıp Dergisi. 2021; 43(6): 609-16. [Crossref]
19. Lachmann HJ, Sengül B, Yavuzşen TU, et al. Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford). 2006; 45(6): 746-50. [Crossref]

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RESEARCH ARTICLE

Clinical and radiological comparison of single and double-plate fixation in comminuted clavicular shaft fractures

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ABSTRACT

Aim: In this study, we compared the single-plate technique (with suturing of small fragments) and the double-plate technique, that we applied to patients who underwent surgery for comminuted clavicle fractures, in terms of fracture healing, early return to work, and the need for secondary surgery due to plate irritation.

Materials and Methods: All patients who underwent surgery due to clavicle fracture between 2018 and 2023 were evaluated retrospectively. A total of 107 patients who came for regular check-ups and were under our follow-up were evaluated. Fifteen patients with comminuted shaft fractures who were fixed with a 3.5 mm plate superiorly and a 2.4 mm mini plate anteriorly, and 19 patients who were fixed with a 3.5 mm single-plate superiorly and 2.0 Ethibond sutures, were included in the study. Patients were divided into two groups according to single/double-plate application. Patients in Group 1 received a 3.5 mm Locking Compression Plate (LCP) single-plate application superiorly followed by a doubled-suture Nice knot (described by Boileau et al.) (Figure 1). In Group 2, patients received a superior 3.5 mm LCP plate followed by an anterior 2.4 mm mini plate (Figure 2).

Results: Significant differences were observed between patients with single-plate and double-plate applications in terms of various clinical recovery times, return to work times, and plate removal requirements. The clinical recovery time was significantly faster in the double-plate group [6 (IQR: 5-7) weeks vs. 4 (IQR: 4-5) weeks, $p < 0.001$]. The time to return to work was similarly shorter in the double-plate group [8 (IQR: 7-8) weeks vs. 7 (IQR: 6-7) weeks, $p = 0.001$]. The need for plate removal was significantly higher in the double-plate group ($p = 0.016$), with 73.3% (n=11/15) of patients requiring plate removal, compared to 31.6% (n=6/19) in the single-plate group.

Conclusion: In addition to superior plating in the fixation of comminuted clavicle fractures, the application of a mini plate from the anterior for fixation of the butterfly fragment allows for earlier rehabilitation and a rapid return to work. However, the risk of a second operation due to plate irritation should also be considered. No negative effect of fixation of small fragments with sutures on fracture union was observed. If the situation of the soft tissue is not well, a single-plate can be used in comminuted fractures. However, in cases where fixation is not enough, double-plate is a procedure that can be applied safely.

Keywords: Clavicle, double-plate application, fracture, outcome

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INTRODUCTION

Clavicle shaft fractures are serious injuries that typically occur in active individuals due to a direct blow to the shoulder. Although the traditional view is to treat conservatively, it results in a 15% rate of nonunion, malunion, and decreased functional capacity (1). While most clavicle fractures are treated conservatively, severely displaced or comminuted fractures may require surgical fixation. The most commonly preferred surgical treatment is the 3.5 mm Locking Compression Plate (LCP). Other fixation options are intramedullary pinning with Kirschner wires, cannulated screws, compression plates, precontoured clavicle locking plates, and external fixation (2). Although these techniques are sufficient for fixation of the main fragments in the distal and proximal areas, they are inadequate for the fixation of small fragments in the fracture line.

It is difficult to fix small fragments in the fracture line with a lag screw, as it often leads to bone fragmentation. In surgical practice, these fragments can be tied using absorbable sutures (3), or anterior plating (4) can be added to the procedure to solve these problems.

Biomechanical studies have shown that dual plating techniques using mini-fragment plates have superior biomechanical properties compared to single superior/anterior plating techniques (5). Despite this biomechanical superiority, there are comparative clinical and radiological studies indicating that there is no difference in healing rates between patient groups (6). An important consideration when evaluating early fracture healing and return to work in clavicle fractures is plate irritation and the need for secondary surgery. This rate is reported as 9-64% in the literature (7,8).

In this study, we compared the single-plate technique (with suturing of small fragments) and the double-plate technique, that we applied to patients who underwent surgery for comminuted clavicle fractures, in terms of fracture healing, early return to work, and the need for secondary surgery due to plate irritation.

MATERIALS AND METHODS

Before starting the study, Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee Approval was received (No: 2020/238 Date: 29/09/2020). All patients who underwent surgery due to clavicle fracture between 2018 and 2023 were evaluated retrospectively. A total of 107 patients who came for regular check-ups and were under our follow-up were evaluated. Fifteen patients with comminuted shaft fractures who were fixed with a 3.5 mm plate superiorly and a 2.4 mm mini plate anteriorly, and 19 patients who were fixed with a 3.5 mm single-plate superiorly and 2.0 Ethibond sutures, were included in the study. Patients with two-part fractures, patients using different implants, patients who smoke, patients using drugs that may impair fracture healing (such as steroids, NSAIDs, quinolones, bisphosphonates), and patients lost to follow-up due to irregular check-ups were excluded from the study.

Patients were divided into two groups according to single/double-plate application. Patients in Group 1 received a 3.5 mm LCP single-plate application superiorly followed by a doubled-suture Nice knot (described by Boileau et al.) (Figure 1) (9). In Group 2, patients received a superior 3.5 mm LCP plate followed by an anterior 2.4 mm mini plate (Figure 2).

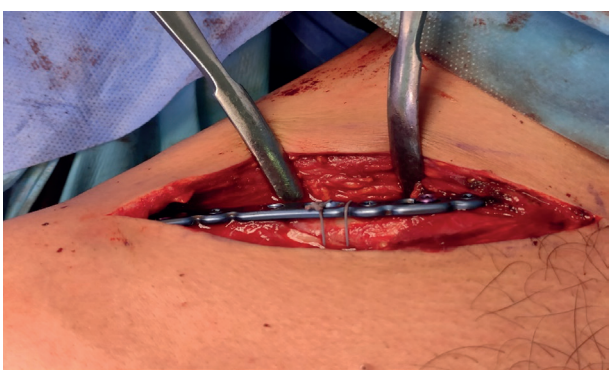

Figure 1. Single-plate application followed by a double-suture.

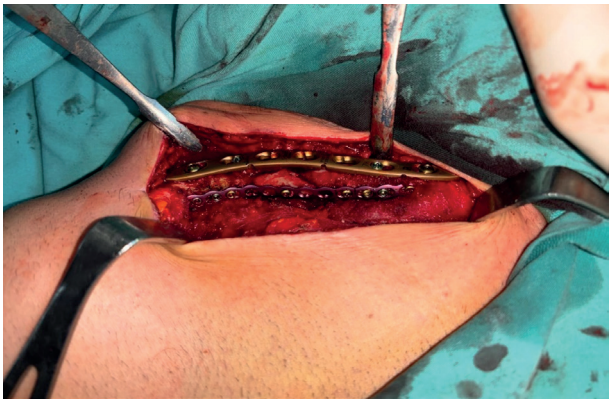

Figure 2. Anterior and superior plate application.

Postoperatively, a velpeau bandage was applied for one month, and elbow and passive range of motion exercises were started. After 30 days, the bandage was removed, and active range of motion exercises were started. After the third month, strengthening exercises were started.

The condition of the patients who came for regular monthly check-ups in the postoperative period was recorded. Patients who did not have pain in the fracture line were considered to have clinical union. Radiological union was accepted when three cortex continuity was detected in the anteroposterior and 45° oblique radiographs taken during the controls. In addition, the time taken for the patients to return to work, the need for a second operation due to plaque irritation, and the presence of infection were also evaluated. Annual controls were performed after six months postoperatively.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median [Interquartile range (IQR): 25th - 75th percentile], and categorical variables were presented as frequency and percentage (%). The normality distribution of continuous variables was assessed using the Shapiro-Wilk test. To assess differences between two independent groups, the independent sample t-test was used for continuous variables with normal distribution, and the Mann-Whitney U test was used for variables without normal distribution. Differences between categorical variables were analyzed using Pearson's chi-square test. All statistical analyses were performed using SPSS 26.0 and the significance level was set at $p < 0.05$.

RESULTS

According to the results of Table 1, significant differences were observed between patients with single-plate and double-plate applications in terms of various clinical recovery times, return to work times, and plate removal requirements. The clinical recovery time was significantly faster in the double-plate group [6 (IQR: 5-7) weeks vs. 4 (IQR: 4-5) weeks, $p < 0.001$]. The time to return to work was similarly shorter in the double-plate group [8 (IQR: 7-8) weeks vs. 7 (IQR: 6-7) weeks, $p = 0.001$]. The need for plate removal

Table 1. Comparison of patients with single and double-plate application

Variables	Group 1 (n=19)	Group 2 (n=15)	p
Age (year)	42.7 ± 12.1	39.7 ± 11.3	0.472
Follow-up period (week)	33.8 ± 6.6	35.3 ± 5.9	0.520
Clinical union (week)	6 (5 - 7)	4 (4 - 5)	**<0.001**
Radiological union (week)	16 (12 - 16)	16 (12 - 16)	0.758
Return to work(week)	8 (7 - 8)	7 (6 - 7)	**0.001**
Implant removal			**0.016**
No	13 (%68.4)	4 (%26.7)	
Yes	6 (%31.6)	11 (%73.3)	

Data are summarized as mean ± SD, median (25th–75th percentile) and n(%) values. Bold p-values indicate statistical significance for Mann-Whitney U test or Pearson's chi-square test.

was significantly higher in the double-plate group (p=0.016), with 73.3% (n=11/15) of patients requiring plate removal, compared to 31.6% (n=6/19) in the single-plate group.

DISCUSSION

Among the various fixation options used in the surgical treatment of clavicle fractures, superior LCP plates are the most commonly used implant. Nonunion, delayed union, implant failure, infection, and brachial plexus injury are expected complications. Possible risk factors for construct failure include implant type and fracture type. In particular, fixation failure is observed in 5-7% of cases due to poor bone quality and inadequate technique (10,11).

Kitzen et al. compared the superior single 3.5 mm plate application with different double-plate applications. In terms of axial stiffness, the application of a double-plate consisting of a 2.4 mm superior and a 2.7 mm anterior plate was found to be significantly superior. No difference was observed between the different implant combinations in terms of torsional stiffness or load to failure (5). Boyce et al. conducted a biomechanical study comparing a 3.5 mm superior plate, a 3.5 mm superior + 2.8 mm anterior plate, and two 2.8 mm mini plates. According to the results of the study, double orthogonal fixation with mini plates showed lower stiffness and durability than traditional superior 3.5 mm plate fixation. The addition of an anterior miniplate to the traditional superior 3.5 mm plate fixation improved construct stiffness and may play a role in patients seeking an early return to activity (12). Similar results were found in this study. Patients in the double-plate group were found to return to work significantly earlier.

Clinically, it is emphasized that the fracture healing rates of single-plate and double-plate applications are similar, 2.9% vs. 0.8%, respectively. Complication rates such as infection and neurovascular injury are also similar (5). It is emphasized in the literature that the need for a second operation due to implant irritation is higher in 3.5 mm plates placed superiorly, with a rate of 30% (13). The application of small fragment plates by contouring increases the need for secondary surgery due to implant irritation from 8% to 20% (9). In this study, plate irritation rates were found to be higher in the patient group that received double-plates.

Fixation of free bone fragments in the shaft poses a serious problem due to insufficient cortical support. Although most authors recommend lag screw fixation after reduction for these fragments, it results in inadequate fixation due to fragmentation of the bone tissue (14). The doubled-suture Nice knot described by Boileau et al. is another current fixation technique used. 2.0 Ethibond sutures with locked sliding knots are semi-stable but can be easily applied (15). Wu et al. retrospectively followed 56 patients who underwent suture-knotted plate fixation for a mean of 25.6 months. They reported that bone healing was complete in all patients. They also emphasized that the combination of the suture knots and plate screws fixation technique is reliable and effective (16).

This study had several limitations. Although the small number of patients and the retrospective design are shortcomings of the study, the fact that all surgeries and patient follow-ups were performed by the same researcher is an advantage.

In conclusion, in addition to superior plating in the fixation of comminuted clavicle fractures, the application of a mini plate from the anterior for fixation of the butterfly fragment allows for earlier rehabilitation and a rapid return to work. However, the risk of a second operation due to plate irritation should also be considered. No negative effect of the fixation of small fragments with sutures on fracture union was observed.

Ethical approval

This study has been approved by the Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee (approval date 29/09/2020, number 2020/238). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: TA, HAÜ; Concept: TA, HAÜ, OK; Design: TA, HAÜ, OK; Data Collection or Processing: TA, HAÜ; Analysis or Interpretation:

OK; Literature Search: TA; Writing: TA, HAÜ, OK. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

REFERENCES

1. Bhardwaj A, Sharma G, Patil A, Rahate V. Comparison of plate osteosynthesis versus non-operative management for mid-shaft clavicle fractures-A prospective study. Injury. 2018; 49(6): 1104-7. [Crossref]
2. Zhuang Y, Zhang Y, Zhou L, Zhang J, Jiang G, Wu J. Management of comminuted mid-shaft clavicular fractures: Comparison between dual-plate fixation treatment and single-plate fixation. J Orthop Surg (Hong Kong). 2020; 28(2): 2309499020915797. [Crossref]
3. Ju WN, Wang CX, Wang TJ, Qi BC. Fixation of comminuted midshaft clavicle fractures with bone fragments separated by soft tissue using a novel double ligature technique: A case report. Medicine (Baltimore). 2017; 96(45): e8606. [Crossref]
4. Zielinski E, Doe K, Perdue P. Dual Plate Minifragment Fixation of Clavicle Fractures- Technique and Approach. J Orthop Trauma. 2022; 36(Suppl 3): S1-2. [Crossref]
5. Kitzen J, Paulson K, Korley R, Duffy P, Martin CR, Schneider PS. Biomechanical Evaluation of Different Plate Configurations for Midshaft Clavicle Fracture Fixation: Single Plating Compared with Dual Mini-Fragment Plating. JB JS Open Access. 2022; 7(1): e21.00123. [Crossref]
6. Charles SJ, Kumar P, Reddy RP, et al. Dual Versus Single Plate Fixation of Displaced Midshaft Clavicle Fractures: A Cost-Effectiveness Analysis. J Bone Joint Surg Am. 2023; 105(23): 1886-96. [Crossref]
7. Leroux T, Wasserstein D, Henry P, et al. Rate of and Risk Factors for Reoperations After Open Reduction and Internal Fixation of Midshaft Clavicle Fractures: A Population-Based Study in Ontario, Canada. J Bone Joint Surg Am. 2014; 96(13): 1119-25. [Crossref]
8. Wijdicks FJG, Van der Meijden OAJ, Millett PJ, Verleisdonk EJMM, Houwert RM. Systematic review of the complications of plate fixation of clavicle fractures. Arch Orthop Trauma Surg. 2012; 132(5): 617-25. [Crossref]
9. Sheth U, Fernandez CE, Morgan AM, Henry P, Nam D. Are two plates better than one? A systematic review of dual plating for acute midshaft clavicle fractures. Shoulder Elbow. 2022; 14(5): 500-9. [Crossref]
10. DeBaun MR, Chen MJ, Campbell ST, et al. Dual Mini-Fragment Plating Is Comparable With Precontoured Small Fragment Plating for Operative Diaphyseal Clavicle Fractures: A Retrospective Cohort Study. J Orthop Trauma. 2020; 34(7): e229-32. [Crossref]
11. Meeuwis MA, Pull Ter Gunne AF, Verhofstad MHJ, van der Heijden FHWM. Construct failure after open reduction and plate fixation of displaced midshaft clavicular fractures. Injury. 2017; 48(3): 715-9. [Crossref]
12. Boyce GN, Philpott AJ, Ackland DC, Ek ET. Single versus dual orthogonal plating for comminuted midshaft clavicle fractures: a biomechanics study. J Orthop Surg Res. 2020; 15(1): 248. [Crossref]
13. Allis JB, Cheung EC, Farrell ED, Johnson EE, Jeffcoat DM. Dual Versus Single-Plate Fixation of Midshaft Clavicular Fractures: A Retrospective Comparative Study. JB JS Open Access. 2020; 5(2): e0043. [Crossref]
14. Drosdowech DS, Manwell SEE, Ferreira LM, Goel DP, Faber KJ, Johnson JA. Biomechanical analysis of fixation of middle third fractures of the clavicle. J Orthop Trauma. 2011; 25(1): 39-43. [Crossref]
15. Boileau P, Alami G, Rumian A, Schwartz DG, Trojani C, Seidl AJ. The Doubled-Suture Nice Knot. Orthopedics. 2017; 40(2): e382-6. [Crossref]
16. Wu G, Chen YQ, Chen CY, et al. Clinical outcomes of doubled-suture Nice knot augmented plate fixation in the treatment of comminuted midshaft clavicle fracture. BMC Surg. 2021; 21(1): 270. [Crossref]

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RESEARCH ARTICLE

Retrospective evaluation of cases with pneumothorax in our neonatal intensive care unit

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ABSTRACT

Aim: This study aimed to retrospectively evaluate the patients who were followed up in the neonatal intensive care unit of our hospital with the diagnosis of pneumothorax.

Methods: The records of patients who were followed up with the diagnosis of pneumothorax in our neonatal intensive care unit between September 1, 2016 and December 31, 2022 were retrospectively reviewed. Birth weight, sex, gestational week, mode of delivery, localization of pneumothorax, presence of underlying primary lung disease, and mortality were evaluated.

Results: The mean birth weight of 35 patients (19 girls, 16 boys) who developed pneumothorax was 2200±1050 g and the mean gestational age was 33.2±5.1 weeks. Twenty-seven of the patients were delivered by cesarean section and 8 by normal spontaneous vaginal delivery. Pneumothorax was most common on the right side (n:19) and no patient had bilateral pneumothorax. 13 patients had received surfactant treatment before pneumothorax. The primary diagnoses were respiratory distress syndrome (RDS) in 17 patients and transient tachypnea of the newborn (TTN) in 11 patients. 14 patients were resuscitated at birth. A thoracic tube was inserted in 22 patients, while 13 patients were followed up conservatively.

Conclusions: The most common predisposing causes in patients with pneumothorax are RDS and TTN. Early diagnosis and treatment of pneumothorax is life-saving. It should be kept in mind that pneumothorax may develop in patients who are followed up in the neonatal intensive care unit due to respiratory distress.

Keywords: Neonatal intensive care unit, neonate, pneumothorax

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INTRODUCTION

Pneumothorax is defined as lung collapse secondary to the presence of air in the space between the parietal and visceral pleura (1). Depending on the extent of lung collapse, the pneumothorax may be partial or complete, unilateral or bilateral. While partial pneumothoraxes with a small amount of air are generally asymptomatic and spontaneously absorbed by the body, pneumothoraxes with a large amount of air can be fatal in the neonatal period (2,3).

The gold standard diagnostic method for pneumothorax is radiologic demonstration of air in the pleural space. The use of lung ultrasonography has become widespread in recent years. Its sensitivity and specificity are reported to be very high in experienced hands (4-7).

It is most commonly observed in the neonatal period of childhood. Its incidence is 1-2% in term newborns and 6% in preterm newborns. This rate increases up to 30% in those who need mechanical ventilation and have an underlying pulmonary problem (8,9). Pneumothorax, which is one of the major causes of respiratory distress, leads to high mortality and morbidity, especially in premature babies. Therefore, urgent diagnosis and initiation of treatment are very important in terms of mortality and morbidity (10).

In this study, we aimed to retrospectively evaluate the patients who were followed up in the neonatal intensive care unit of our hospital with a diagnosis of pneumothorax.

MATERIAL AND METHODS

The records of patients who were followed up and treated with a diagnosis of pneumothorax in our neonatal intensive care unit between September 1, 2016 and December 31, 2022 were retrospectively reviewed. The study was approved by the Non-Interventional Clinical Research Ethics Committee of Adıyaman University (approval date 15.11.2022, number 2022/8-3). The diagnosis of pneumothorax was confirmed through radiological imaging. Patients whose diagnosis was not confirmed radiologically were excluded from the study. Gestational week, gender, mode of delivery, birth weight, Apgar scores, cardiopulmonary resuscitation (CPR) after delivery, time of pneumothorax onset and symptoms, underlying primary lung disease, localization of pneumothorax, type of oxygen and respiratory support before and after the diagnosis of pneumothorax, surfactant administration and their association with mortality were evaluated. The decision to insert a chest tube was based on the patient's clinical condition. Babies with a gestational week less than thirty-seven weeks were considered preterm, while those with a gestational age of thirty-seven weeks or more were considered term.

Statistical analyses

Statistical analyses were performed using SPSS version 25 (IBM Corp. Released in 2017. IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.) package program. Descriptive statistics were used to present the frequencies and ratios of individuals in the groups with respect to various variables. Chi-square analysis or Fisher exact test was used to compare categorical variables. The significance level was set at as $p < 0.05$ for all analyses.

RESULTS

Of the 35 patients with pneumothorax, 19 (54.3%) were female and 16 (45.7%) were male. The mean birth weight of the patients was 2200±1050 g and the mean gestational age was 33.2±5.1 weeks. Eight (22.9%) patients had a normal delivery and 27 (77.1%) patients had a cesarean section. In 16 (45.7%) patients the Apgar score at 1 minute was less than 7. In 9 (25.7%) of these patients, the 5th minute Apgar score remained below 7. Thirteen (37.1%) patients received surfactant treatment before pneumothorax. In 19 (54.3%) patients the localization of the pneumothorax was on the right side and no patient developed bilateral pneumothorax. There was no difference between term and preterm infants in terms of gender, mode of delivery, Apgar score, surfactant requirement, and site of pneumothorax (Table 1). When the primary diagnoses of patients with pneumothorax were analyzed, respiratory distress syndrome (RDS) was observed with the highest rate (48.6%, n=17). 11 (31.4%) patients had transient tachypnea of the newborn (TTN). Neonatal pneumonia and congenital

diaphragmatic hernia were observed in 2 (5.7%) patients each, while spontaneous pneumothorax, meconium aspiration syndrome (MAS) and non-immune hydrops were observed in 1 (2.9%) patient each (Table 2). Early respiratory characteristics and clinical outcomes of patients with pneumothorax were analyzed. Fourteen (40%) patients were resuscitated at birth. During resuscitation, Positive pressure ventilation (PPV)+intubation was performed in 13 (37.1%) patients and PPV+chest compression in 3 (8.6%) patients. There was no significant difference between preterm and term babies in terms of resuscitation and

Table 1. Demographic characteristics of cases with pneumothorax

	Total n (%)	Preterm n (%)	Term n (%)	p
Gender				
Female	19 (54.3)	13 (59.1)	6 (46.2)	0.458
Male	16 (45.7)	9 (40.9)	7 (53.8)	
Delivery				
Vaginal	8 (22.9)	4 (18.2)	4 (30.8)	0.397
Cesarean Section	27 (77.1)	18 (81.8)	9 (69.2)	
Apgar score 1. min.				
<7	16 (45.7)	11 (50)	5 (28.5)	0.508
≥7	19 (54.3)	11 (50)	8 (61.5)	
Apgar score at 5 min.				
<7	9 (25.7)	6 (27.3)	3 (23.1)	0.783
≥7	26 (74.3)	16 (72.7)	10 (76.9)	
Surfactant requirement				
Yes	13(37.1)	10 (45.5)	3 (23.1)	0.178
No	22 (62.9)	12 (54.5)	10 (76.9)	
Location of Pneumothorax				
Right	19 (54.3)	13 (59.1)	6 (46.2)	0.458
Left	16 (45.7)	9 (40.9)	7 (53.8)	

Table 2. Primary diagnoses of cases with pneumothorax

Diagnoses	Total n (%)	Preterm n (%)	Term n (%)
Spontaneous pneumothorax	1 (2.9)	1(4.5)	0 (0)
Transient tachypnea of the newborn (TTN)	11 (31.4)	3 (13.6)	8 (61.5)
Respiratory distress syndrome (RDS)	17 (48.6)	16 (72.7)	1 (7.7)
Neonatal pneumonia	2 (5.7)	0 (0)	2 (15.4)
Meconium aspiration syndrome (MAS)	1 (2.9)	0 (0)	1(7.7)
Congenital diaphragmatic hernia	2 (5.7)	1 (4.5)	1(7.7)
Nonimmune hydrops	1 (2.9)	1 (4.5)	0 (0)
Total	35 (100)	22 (100)	13 (100)

Table 3. Early respiratory characteristics and clinical outcomes in neonates with pneumothorax

		Total n (%)	Preterm n (%)	Term n (%)	p
Resuscitation at birth	yes	14 (40)	10 (45.5)	4 (30.8)	0.392
	no	21 (60)	12 (54.5)	9 (69.2)	
Resuscitation (PPV)	yes	14 (40)	10 (45.5)	4 (30.8)	0.392
	no	21 (60)	12 (54.5)	9 (69.2)	
Resuscitation (PPV+ intubation)	yes	13 (37.1)	10 (45.5)	3 (23.1)	0.336
	no	22 (62.9)	12 (54.5)	10 (76.9)	
Resuscitation (chest compression)	yes	3 (8.6)	2 (9.1)	1 (7.7)	0.886
	no	32 (91.4)	20 (90.9)	12 (92.3)	

PPV: Positive Pressure Ventilation

Table 4. Respiratory and clinical characteristics at the time of pneumothorax diagnosis

		Total	Preterm	Term	p
Respiratory support before pneumothorax	Oxygen	4 (11.4)	2 (9.1)	2 (15.4)	0.728
	NIV	12 (34.3)	7 (31.8)	5 (38.5)	
	MV	19 (54.3)	13 (59.1)	6 (46.2)	
Respiratory support after pneumothorax	Continue with oxygen	4 (11.4)	2 (9.1)	2 (15.4)	0.861
	Continue with NIV	3 (8.6)	2 (9.1)	1 (7.7)	
	Transition to MV	9 (25.7)	5 (22.7)	4 (30.8)	
	Continue with MV	19 (54.3)	13 (59.1)	6 (46.2)	

MV: Mechanical ventilation; NIV: Non-invasive ventilation

observable clinical characteristics (Table 3). When analyzing the respiratory status of the patients before and after pneumothorax, it was found that 4 (11.4%) patients received free oxygen, 12 (34.3%) patients received noninvasive ventilation (NIV) support, and 19 (54.3%) patients received invasive mechanical ventilation (IMV) support before pneumothorax. After pneumothorax, 4 (11.4 %) patients continued with free oxygen, 3 (8.6 %) patients continued with NIV, 9 (25.7 %) patients switched to IMV, and 19 (54.3 %) patients continued with IMV. There was no statistically significant difference between respiratory support received before pneumothorax and respiratory support received after pneumothorax in preterm and term infants (Table 4).

DISCUSSION

Pneumothorax is most commonly observed in the neonatal period, especially in the first 72 hours after birth (11). The reason for its frequent occurrence in the neonatal period is the high pressure in the lungs with the onset of respiration (12). While its incidence in all live births is between 0.08% and 0.14%, this rate increases to between 1% and 6% in babies followed in the intensive care unit during the neonatal period (3,13). In our study, the incidence of pneumothorax was found to be 0.12% among all live births and this rate was compatible with the literature. In a study conducted by Özbek et al. (14) with 112 patients, it was reported that pneumothorax developed in the

first 48 hours in 76% of the patients, and in a study conducted by Akdoğan et al. (15), it was reported that pneumothorax developed in the first 48 hours in 100% of the patients. In our study, 91.4% of our patients developed pneumothorax in the first 72 hours.

Pneumothorax may present with a severe picture including dyspnea, severe tachypnea, subcostal, intercostal retractions, and cyanosis, or it may present with mild symptoms including only an increase in respiratory rate (16). Pneumothorax should be considered in cases presenting with decreased oxygen saturation, sudden onset of respiratory distress, the need to increase ventilator settings, or absent breath sounds on auscultation (17). Pneumothorax may be secondary to underlying lung pathology (such as RDS, meconium aspiration syndrome, pulmonary hypoplasia), resuscitation at birth, positive pressure mechanical ventilation, or may occur spontaneously (8,9). It is known that pneumothorax is more common in premature and cesarean born babies. Its frequent occurrence in premature infants has been attributed to their need for respiratory support due to respiratory problems (18,19). Cesarean section is known to predispose to pneumothorax by causing RDS and TTN (20). The two most common risk factors for pneumothorax in our patients were TTN and RDS. RDS was the most common primary diagnosis in preterm babies, and TTN was the most common primary diagnosis in term babies. In the study by Çördük et al. (21), 63% of the patients were preterm and the most common causes of pneumothorax were reported as RDS and TTN. In our study, 63% of the patients were preterm infants and the rate was similar to the literature.

Patients receiving mechanical ventilation and positive pressure ventilation are more likely to develop pneumothorax. High pressure causes pneumothorax by causing barotrauma (22). In a study conducted by Malek et al. (9) on 400 neonatal patients receiving mechanical ventilation, it was reported that 26% of the patients developed pneumothorax. In our study, 54.2% of the patients were receiving IMV support, 34.3% were receiving NIV support, and 11.4% were receiving free oxygen before the development of pneumothorax. Our findings support the literature and reveal that mechanical ventilation is an important risk factor for pneumothorax.

Pneumothorax is frequently unilateral and is most commonly seen on the right side (22). Navaei et al. (23) found that pneumothorax was located on the right side in 57%, on the left side in 40%, and bilateral in 3%. In our study, 54.3% of the pneumothorax was right localized, 45.7% was left localized, and no patient developed bilateral pneumothorax. Our results are similar to the study of Navaei et al.

Although rare, pneumothorax is a condition with high mortality if diagnosis and treatment are delayed (24). Pneumothorax increases the length of hospital stay, the need for mechanical ventilation, and mortality (22). Currently, mortality rates of 20-60% are reported. The earlier the onset of pneumothorax, the higher the mortality rate. In particular, pneumothorax that develops within the first 24 hours of life has a mortality rate of up to 60% (11,16). Patients with accompanying lung parenchymal disease are known to have a worse prognosis. The mortality rate increases with decreasing gestational age and birth weight. Mortality is especially high in preterm infants with gestational age less than 29 weeks (10,11). In our study, 12 patients were lost (mortality rate 34%). Seventy-five percent of the lost patients were preterm, and our mortality rates were compatible with the literature.

In conclusion, pneumothorax most commonly develops in the neonatal period and usually occurs within the first 72 hours of life. The most common cause is TTN in term babies and RDS in preterm babies. Pneumothorax, defined as air entering between the parietal and visceral pleura, which is one of the air leak syndromes, should be considered in the event of sudden deterioration in general condition, increased retractions, cyanosis and bradycardia in infants monitored in the neonatal intensive care unit for respiratory distress. It should be noted that morbidity and mortality are reduced with prompt and effective treatment.

Ethical approval

This study has been approved by the Adıyaman University Non-Interventional Clinical Research Ethics Committee (approval date 15/11/2022, number 2022/8-3). Written informed consent was obtained from the participants.

Author contribution

Concept: AA, SA; Design: AA, SA; Data Collection or Processing: AA, SA; Analysis or Interpretation: AA, SA; Literature Search: AA, SA; Writing: AA, SA. All authors reviewed the results and approved the final version of the article.

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REFERENCES

1. Zarogoulidis P, Kioumis I, Pitsiou G, et al. Pneumothorax: from definition to diagnosis and treatment. J. Thorac. Dis. 2014;6:S372-S376
2. Park SW, Yun BH, Kim KA, Ko Sy, Lee YK, Shin SM. A clinical study about symptomatic spontaneous pneumothorax. Korean J Perinatol. 2006; 17: 304-9.
3. Vibede L, Vibede E, Bendtsen M, Pedersen L, Ebbesen F. Neonatal pneumothorax: a descriptive regional Danish study. Neonatology. 2017; 111(4): 303-8. **[Crossref]**
4. Cattarossi L, Copetti R, Brusa G, Pintaldi S. Lung ultrasound diagnostic accuracy in neonatal pneumothorax. Can Respir J. 2016; 2016: 6515069. **[Crossref]**
5. Liu J, Chi JH, Ren XL, et al. Lung ultrasonography to diagnose pneumothorax of the newborn. Am J Emerg Med. 2017; 35(9): 1298-302. **[Crossref]**
6. Jhaveri V, Vali P, Giusto E, Singh Y, Lakshminrusimha S. Pneumothorax in a term newborn. J Perinatol. 2024; 44(4): 465-71. **[Crossref]**
7. Sabour S. Ultrasound of pneumothorax in neonates: diagnostic value of the anterior transverse plane and of mirrored ribs; methodological issues. Pediatr Pulmonol. 2022; 57(9): 2257-8. **[Crossref]**
8. Litmanovitz I, Carlo WA. Expectant management of pneumothorax in ventilated neonates. Pediatrics. 2008; 122(5): e975-9. **[Crossref]**
9. Malek A, Afzali N, Meshkat M, Yazdi NH. Pneumothorax after mechanical ventilation in newborns. Iran J Pediatr. 2011; 21: 45-50.
10. Bhatia R, Davis PG, Doyle LW, Wong C, Morley CJ. Identification of pneumothorax in very preterm infants. J Pediatr. 2011; 159(1): 115-20. **[Crossref]**
11. Apiliogullari B, Sunam GS, Ceran S, Koc H. Evaluation of neonatal pneumothorax. J Int Med Res. 2011; 39(6): 2436-40. **[Crossref]**
12. Al Tawil K, Abu-Ekteish FM, Tamimi O, Al Hathal MM, Al Hathlol K, Abu Laimun B. Symptomatic spontaneous pneumothorax in term newborn infants. Pediatr Pulmonol. 2004; 37(5): 443-6. **[Crossref]**
13. Trevisanuto D, Doglioni N, Ferrarese P, Vedovato S, Cosmi E, Zanardo V. Neonatal pneumothorax: comparison between neonatal transfers and inborn infants. J Perinat Med. 2005; 33(5): 449-54. **[Crossref]**
14. Özbek AS, Kavuncuoğlu S, Ugan Atik S, Aldemir EY, Payaslı M, Sander S. Investigation of cases followed up with the diagnosis of pneumothorax in the neonatal intensive care unit between 2004-2008. Journal of Gynaecology Obstetrics Pediatrics and Pediatric Surgery. 2011: 3(2): 79-85.
15. Akdoğan Z, Ovalı F, Samancı N, Dağoğlu T, Boneval C, Aksöyek S. Frequency of pneumothorax in newborns with respiratory distress. Türkiye Klinikleri Pediatri Dergisi. 1996; 5: 68-71.
16. Ali R, Ahmed S, Qadir M, Maheshwari P, Khan R. Pneumothoraces in a neonatal tertiary care unit: case series. Oman Med J. 2013; 28(1): 67-9. **[Crossref]**
17. Alice Z, Gündogdu G, Kara C, Ilikkan B, Celayir S. Which patients are at risk? Evaluation of the morbidity and mortality in newborn pneumothorax. Indian Pediatr. 2003; 40: 325-8.
18. Aly H, Massaro A, Acun C, Ozen M. Pneumothorax in the newborn: clinical presentation, risk factors and outcomes. J Matern Fetal Neonatal Med. 2014; 27(4): 402-6. **[Crossref]**
19. Kolås T, Saugstad OD, Daltveit AK, Nilsen ST, Øian P. Planned cesarean versus planned vaginal delivery at term: comparison of newborn infant outcomes. Am J Obstet Gynecol. 2006; 195(6): 1538-43. **[Crossref]**
20. Jovandaric MZ, Milenkovic SJ, Dotlic J, et al. Neonatal pneumothorax outcome in preterm and term newborns. Medicina (Kaunas). 2022; 58(7): 965. **[Crossref]**
21. Çördük N, Ürey T, Küçüktaşçı K, et al. Evaluation of newborn with pneumothorax. Pamukkale Medical Journal. 2014; 7(1): 47-51.
22. Türkmen M, Tanmış AÇ, Etensel B, Özkısacık S, Akdilli A, Gürsoy H. Evaluation of cases with pneumothorax followed in the neonatal unit. Journal of Adnan Menderes University Faculty of Medicine. 2010: 11(1): 31-4.
23. Navaei F, Aliabadi B, Moghtaderi M, Kelishadi R. Predisposing factors, incidence and mortality of pneumothorax in a neonatal intensive care unit in Isfahan, Iran. Chinese Journal of Contemporary Pediatrics. 2010; 12(6): 417-20.
24. Thomas NH, Anthony C, Alfred LG, Alicia AM. Principles of respiratory monitoring and therapy. In: Taeusch W, Ballard R, Gleason C, editors. Avery's Diseases of the Newborn. 8th ed. Philadelphia: Elsevier Saunders; 2005: 662-3.

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RESEARCH ARTICLE

Evaluation of pulmonary embolism patients in a tertiary hospital with clinical, radiological and laboratory features

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ABSTRACT

Objective: Pulmonary thromboembolism (PTE) presents with a wide range of symptoms, outcomes, and radiographic features. We evaluated the clinical, laboratory, and radiological features of PTE.

Materials and Methods: A retrospective study was conducted on patients diagnosed with pulmonary thromboembolism (PTE) between 2019 and 2021 at the Department of Chest Diseases, Abant Izzet Baysal University Hospital. Patients with suspected acute PTE and those diagnosed with pulmonary embolism based on CT angiography were included. Patients with chronic PTE, as diagnosed by ventilation/perfusion scintigraphy, were excluded.

Results: Of the 100 patients included, 42% were female and 58% were male. The mean age of the patients was 70.50 ± 13.54 years. The most common symptom was dyspnea, followed by cough and chest pain. Troponin I levels were elevated in 62 individuals. D-dimer concentrations of all patients were above the upper limit of 0.55 mg/L. Massive PTE was seen in 15% of patients, submassive PTE in 40%, and non-massive PTE in 45%. In addition, systolic pulmonary artery pressure (sPAP) was high in 67% of the cases. Patients with elevated sPAP had a higher mean age, had received more thrombolytic therapy, and had a higher rate of major and submassive pulmonary embolisms. Troponin I values were seen to be elevated in massive PTE, as expected (p=0.024). D-dimer values were significantly higher in patients with pulmonary embolism in the main branch (p=0.018).

Conclusion: In light of the data we obtained from our study, we believe that a detailed cardiovascular system evaluation, including Troponin I and systolic pulmonary artery pressure measurements, is very important in the diagnosis process and in predicting the prognosis after diagnosis in patients presenting with suspected pulmonary thromboembolism.

Keywords: D-dimer, pulmonary embolism, systolic pulmonary artery pressure

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INTRODUCTION

Pulmonary thromboembolism (PTE) occurs when one or more thrombi, typically originating from the deep veins of the lower and upper extremities, migrate from the systemic circulation to the pulmonary vascular bed (1,2). PTE and deep vein thrombosis are different manifestations of the same pathological process and are collectively referred to as venous thromboembolism (VTE). PTE is the third most common cause of death from cardiovascular conditions, following myocardial infarction and cerebrovascular accident (3-5). Scoring patients with suspected PTE according to their symptoms, findings, laboratory test results, and risk factors, then classifying them as "low, intermediate, or high probability" is useful for empirical diagnosis and treatment approaches. Computed Tomography Pulmonary Angiography (CTPA) is a frequently used and easily accessible imaging tool with high diagnostic accuracy for PTE (6,7). Despite this, PTE still causes high morbidity and mortality; therefore, great importance should be given to the diagnosis and treatment of the disease (8,9). The aim of this study was to evaluate the clinical, laboratory, and radiological findings of patients diagnosed with PTE who presented to the Chest Diseases Clinic of Abant İzzet Baysal Training and Research Hospital.

MATERIALS AND METHODS

In the study, 100 patients who were admitted to the Chest Diseases Department of Abant İzzet Baysal Education and Research Hospital between January 2019 and January 2021 and diagnosed with pulmonary embolism were retrospectively examined. Patients diagnosed with chronic pulmonary thromboembolism, and patients diagnosed with pulmonary thromboembolism via ventilation/perfusion scintigraphy were excluded from the study; only patients diagnosed with acute pulmonary thromboembolism via CTPA were included. The demographic information of all patients diagnosed with acute PTE were documented, including age, gender, presence of concomitant diseases, symptoms at the time of admission, D-dimer and troponin I levels and ECHO findings. When classifying PTE clinically and hemodynamically according to the patient's risk factors, the presence or absence of deep vein thrombosis (DVT) and the location of thromboembolism on CTPA were also taken into consideration. Lower Extremity Venous Doppler Ultrasonography was performed to scan common, deep, superficial and crural veins using Samsung RS 85 device. Pulmonary hypertension was assessed by measuring systolic pulmonary artery pressure (sPAP) via transthoracic echocardiography. It was also noted whether the patients received thrombolytic therapy during their follow-up.

Ethical approval was obtained from the Bolu Abant İzzet Baysal Clinical Research Ethics Committee, and permission was obtained from the Chief Physician of the Bolu Abant İzzet Baysal Training and Research Hospital for the research (Ethics Committee Number: 2022/134).

Since this was a retrospective study, informed patient consent was not required.

The collected data were transferred to a computer for analysis. The results were presented as mean ± standard deviation, frequency and percentage. The Mann-Whitney U test was used to analyse variables between groups. Kruskal-Wallis variance analysis was applied when the number of groups was more than two because it did not comply with the normal distribution. Spearman correlation analysis was used for correlation analysis. The Chi-square test was used to compare categorical variables. In the statistical analysis, the confidence interval was set at 95% and the significance level was set at $p<0.05$.

RESULTS

The mean age of the patients was 70.50 ± 13.54 years. Of the 100 patients, 42 (42%) were female and 58 (58%) we were male. When the accompanying diseases were examined, 66% of patients had an additional disease. These included cancer (18%), hypertension (HT) (18%), chronic obstructive pulmonary disease (COPD) (9%), atrial fibrillation (AF) (8%), heart failure (CHF) (5%), asthma (4%), cerebrovascular accident (CVA) (2%), chronic renal failure (1%) and obesity (1%).

Shortness of breath, which was observed in 70% of the patients, was the most common presenting symptom, followed by chest pain (14%), and cough (3%). In addition, 30% of the patients had DVT and 67% had high sPAP (Table 1).

Table 1. Demographic characteristics–clinical and radiological findings

	Number (n)	Percentage (%)
Gender		
Female	42	42.0
Male	58	58.0
The Average Age(years)	**70.50±13.54**	
DVT		
Yes	30	30.0
No	70	70.0
High sPAP		
Yes	67	67.0
No	33	33.0
Type of Pulmonary Embolism		
Massive	15	15.0
Submassive	40	40.0
Non-massive	45	45.0
Pulmonary Embolism Site		
Major	27	27.0
Segmental	51	51.0
Subsegmental	22	22.0
Complaint		
Shortness of breath	70	70.0
Chest Pain	14	14.0
Cough	3	3.0
Hemoptysis	3	3.0
Syncope	3	3.0
Fatigue	2	2.0
Pain in Leg	2	2.0
Nausea	1	1.0
Stomach Ache	1	1.0
Back Pain	1	1.0

DVT: Deep Vein Thrombosis, sPAP: systolic pulmonary artery pressure.

Table 2. Analysis of D-dimer values by gender and pulmonary embolism distribution

Gender	D-dimer (mg/L)	P
Female	7.26±6.71	0.035
Male	5.57±11.06	
Pulmonary Embolism Site		
Major	9.38±15.36	0.018
Segmental	5.99±6.50	
Subsegmental	3.13± 2.79	

When laboratory test results were compared according to gender, it was found that D-dimer values of female patients were higher than those of male patients (p=0.035). D-dimer values of patients with main branch pulmonary embolism were found to be significantly higher than those with segmental or subsegmental pulmonary embolism (p=0.018) (Table 2).

Although there was no statistically significant difference in age distribution according to the type of pulmonary embolism, the mean age of patients with submassive pulmonary embolism was higher (p=0.051). In addition, D-dimer values of patients with submassive pulmonary thromboembolism were significantly higher than those of patients with massive and non-massive pulmonary embolisms (p=0.011). Troponin I values of patients with massive pulmonary thromboembolism were significantly higher than those of patients with submassive and non-massive pulmonary embolisms (p=0.024) (Table 3).

The mean age of patients with high sPAP was higher than that of patients without high systolic pulmonary artery pressure (p=0.001). In addition, massive and submassive pulmonary embolisms were found to be more prevalent in the high sPAP group (p=0.000001); therefore, they received more thrombolytic therapy (p=0.001). sPAP was significantly higher in those with pulmonary embolism in the main branch (p=0.030), compared to those with segmental (p=0.047) and subsegmental (p=0.009) branches (Table 4).

Table 3. Distribution of age, D-dimer and troponin I by pulmonary embolism type

	Type of Pulmonary Embolism			
	Massive	**Submassive**	**Non massive**	**P**
Age	64.27±13.98	73.75±10.86	69.69±14.90	0.051
D-dimer (µg/L)	4.28±2.25	9.83±13.71	3.79±3.84	0.011
Troponin-I (ng/ml)	209.36±584.64	33.92±71.80	24.65±56.15	0.024

Table 4. Age, PTE type and treatment method according to sPAP

			sPAP		
			High	**Not High**	**P**
Age			73.63±11.41	64.15±15.37	0.001
Thrombolytic	**Received**	n	16	0	0.001
		%	23.9	0.0	
	Not received	n	51	33	
		%	76.1	100	
Type of Pulmonary Embolism	**Massive**	n	14	1	0.000001
		%	20.9	3.0	
	Submassive	n	35	5	
		%	52.2	15.2	
	Nonmassive	n	18	27	
		%	26.9	81.8	
Pulmonary Embolism Site	**Major**	n	23	4	0.03
		%	34.3	12.1	
	Segmental	n	33	18	
		%	49.3	54.5	
	Subsegmental	n	11	11	
		%	16.4	33.3	

PTE: Pulmonary Thrombo Embolism, sPAP: Systolic pulmonary artery pressure.

DISCUSSION

Pulmonary Thromboembolism is a disease with high morbidity and mortality rates despite the increasing possibilities of radiological and laboratory diagnostic methods. Although both scoring and exclusion criteria are used in diagnosis and treatment, managing the disease can be quite complex and challenging due to factors such as age, gender, comorbidities, and smoking. This study aims to discuss the radiological, laboratory, and clinical features of PTE cases diagnosed in a tertiary center where the disease is frequently encountered, and both medical and surgical risk factors coexist, in light of current data.

The annual mean incidence rate of VTE is 23-269 per 100,000 people. PTE primarily affects the elderly. Except for risk factors specific to women, such as pregnancy and oral contraceptive use, the incidence, recurrence, and mortality rates of PTE are similar

between genders (7). Women constituted 42% of the patients in our study. This figure is consistent with the rates published in Turkey (10). Additionally, in line with previous studies, we evaluated whether gender had a significant impact on the risk of pulmonary embolism and found no such association. However, women diagnosed with PTE were found to have higher D-dimer levels compared to men. No statistically significant relationship was found between gender and D-dimer levels in Kaçmaz's thesis study (11). The relevant findings in our study, which are contradictory to previous studies, could be associated with menstrual cycle variations and oral contraceptive use. However, since relevant data could not be collected for this retrospective analysis, this can only be considered as a limitation of the study.

DVT is one of the risk factors for PTE, affecting 30% of patients. In a study conducted in Turkey by Aytemur Solak et al., DVT was detected in 7 of 17 patients diagnosed with PTE (12), while in a study conducted by Hacıevliyagil et al. (13), DVT was detected in 50% of 20 cases using Doppler ultrasonography. Similar to other studies in the literature, DVT was detected in 30% of patients diagnosed with PTE in our study. According to clinical reports, the most common symptoms in patients with PTE are chest discomfort and shortness of breath. In the study conducted by Erbaycu et al., the most common symptoms were shortness of breath (57.1%) and chest discomfort (55.1%) (14). In the study conducted by Solak et al., the most common symptoms were found to be dyspnea (75.9%) and chest pain (50.0%) (12). In our study, chest discomfort was reported in 14% of patients and shortness of breath was present in 70%. The most common causes of these two symptoms are thought to be hypoxia and infarct areas resulting from ventilation/perfusion imbalance.

The prevalence of radiological findings is important in both diagnosis and follow-up of the disease. PTE was detected in the main branch in 27% of patients, segmental in 51% and subsegmental in 22%. In the study by Wouter et al., thrombus was detected in 7.7% of cases in the pulmonary trunk, 14.6% in the main pulmonary arteries, 28.5% in the lobar arteries, 26.9% in the segmental arteries and 22.3% in the subsegmental arteries (15). Another study reported involvement in segmental and larger arteries in 58% of cases, and involvement in subsegmental and smaller arteries in 42% (16). In our study, consistent with previous studies, the frequency of PTE was found to be higher in the main and segmental branches than in the subsegmental branches. This may be due to the lower rate of clinical symptom formation of PTE in the subsegmental branches. When the age distribution according to the types of pulmonary thromboembolism was examined, no statistically significant difference was found. However, the mean age of patients with submassive pulmonary embolisms was higher than that of patients with other types of pulmonary embolisms (p=0.051). In a relevant study, a statistically significant age difference was found between patients in the submassive group and patients in the massive and non-massive groups (17). Similarly, in our study, we evaluated the reason for the higher mean age in the submassive pulmonary embolism type as the possibility of microembolism secondary to immobilization as the age increases.

Cardiological monitoring is crucial for assessing the progression of PTE and guiding treatment decisions, as it is closely associated with disease severity. When we divided our patients into two groups based on sPAP, it was found that the mean age of patients with elevated sPAP (≥25mmHg) was higher than those with normal sPAP (p=0.001). This may be because, with age, vessels lose the ability to demonstrate the elasticity required to resist increasing pressure. In addition, patients with elevated sPAP had higher rates of major (p=0.000259) and submassive (p=0.000005) PTE compared to patients with normal sPAP (p=0.000001). In a study by Bayram, it was reported that the right ventricular diameters of patients with massive and submassive PTE were significantly higher than those of patients with non-massive PTE and the control group. sPAP values were also significantly higher in patients with massive and submassive PTE than in patients with non-massive PTE and in the control group (18). In our study, consistent with findings in the literature, sPAP was found to be higher in patients with massive PTE compared to other types of pulmonary embolism. This may be due to the greater thrombus load in the main branches and more secondary right heart involvement in the massive embolism type. In addition, sPAP was significantly higher in individuals with pulmonary embolism in the main branch (p=0.030) than in the

segmental (p=0.047) and subsegmental branches (p=0.009). According to our study, thromboembolism in the main branch affects the right heart more than embolisms in other locations, thus causing an increase in sPAP.

The two most frequently measured laboratory parameters in PTE are D-dimer and troponin I levels. In our study, D-dimer values were significantly higher in individuals with submassive pulmonary embolism compared to individuals with major or non-massive pulmonary embolism (p=0.011). In Rodoplu's thesis study, the mean D-dimer level was reported as 762.4 ± 889.6 µg /L in the major group, while it was 713.7 ± 353.9 µg/L in the non-massive group. No statistically significant difference was found between the major and non-massive pulmonary embolism groups in terms of D-dimer levels (p> 0.05) (19). The reason for the difference in our study may be that the comorbidities and age factors of the patients could not be standardized according to the type of embolism. While D-dimer and troponin I values are typically expected to be highest in massive PTE according to thrombus burden, their significance in submassive group may indicate the need for closer monitoring of these patients. This suggests that the frequency of follow-up, particularly regarding the potential need for thrombolytic therapy and the risk of developing chronic PTE, should be increased.

CONCLUSION

In our study, d dimer values were found to be significantly higher in patients with elevated troponin I levels and PTE. Troponin I values were found to be higher in patients with massive embolism. The mean age of patients with elevated sPAP was found to be higher.

Ethical approval

This study has been approved by the Bolu Abant İzzet Baysal Clinical Research Ethics Committee (approval date 10/05/2022, number 2022/134). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: EB; Concept: SK; Design: EÖ; Data Collection or Processing: EB; Analysis or Interpretation: EB; Literature Search: EB, EÖ; Writing: EB All authors reviewed the results and approved the final version of the article..

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Grippi MA, Elias JA, Fishman JA, Kotloff RM, Pack AI, Senior RM. Fishman's Pulmonary Diseases and Disorders. McGrowHill; 2015.
2. Torbicki A, Perrier A, Konstantinides S, et al. Acute Pulmonary Embolism Diagnosis and Treatment Guide. Eur Heart J. 2008; 29(18): 2276-315. **[Crossref]**
3. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012; 379(9828): 1835-46. **[Crossref]**
4. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014; 370(15): 1402-11. **[Crossref]**
5. Taş Gülen Ş. Pulmonary Thromboembolism: Definition and Epidemiology SUMMARY. Turkiye Klin J Pulm Med-Special Top. 2016; 9(1): 6.
6. Meinel FG, Nance JW, Schoepf UJ, et al. Predictive Value of Computed Tomography in Acute Pulmonary Embolism: Systematic Review and Meta-analysis. Am J Med. 2015; 128(7): 747-59.e2. **[Crossref]**
7. Turkish Thoracic Association. Turkish Thoracic Society Pulmonary Thromboembolism Diagnosis and Treatment Consensus Report 2021. 2021.
8. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014; 35(43): 3033-80. **[Crossref]**
9. Barco S, Ende-Verhaar YM, Becattini C, et al. Differential impact of syncope on the prognosis of patients with acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2018; 39: 4186-95. **[Crossref]**
10. Özyol G. Eleveted cardiac troponin I in patient with pulmonary embolism [dissertation]. Sivas: Cumhuriyet University; 2009.

11. Kaçmaz B. Retrospective evaluation of hematological parameters of the pulmonary thromboembolism cases related with risk factors and hypercoagulability [dissertation]. Ankara: University of Health Sciences; 2018.

12. Aytemur Solak Z, Gündüz Telli C, Kabaroğlu C, Doğan B, Bayındır Ü, Erdener D. Pulmoner Emboli Tanisinda D- Dimer Testinin Yeri. Solunum Hastalıkları. 2003; 14(1): 11-6.

13. Hacıevliyagil SS, Mutlu LC, Kızkın Ö, Günen H, Gülbaş G. Altmışüç Pulmoner Emboli Olgusunun Retrospektif Değerlendirilmesi. Solunum Hastalıkları. 2004; 15: 15-21.

14. Erbaycu AE, Tuksavul F, Uçar H, Güçlü SZ. Retrospective Evaluation of Forty-nine Pulmonary Embolism Cases. Izmir Chest Diseases Journal. 2004; 18(3): 113-8.

15. de Monyé W, van Strijen MJ, Huisman MV, Kieft GJ, Pattynama PM. Suspected pulmonary embolism: prevalence and anatomic distribution in 487 consecutive patients. Radiology. 2000; 215(1): 184-8. **[Crossref]**

16. Oser RF, Zuckerman DA, Gutierrez FR, Brink JA. Anatomic distribution of pulmonary emboli at pulmonary angiography: implications for cross-sectional imaging. Radiology. 1996; 199(1): 31-5. **[Crossref]**

17. Köyden B. Clinical determinants of pulmonary embolism [dissertation]. Eskişehir: Eskişehir Osmangazi University; 2012.

18. Bayram T. The relationship between the heart heart functions and heart rate variability evalued by echocardiographic evaluation in patients with acute pulmonary embolism [dissertation]. İstanbul: Marmara University; 2018.

19. Rodoplu E. Correlation of plasma D-dimer level and severity of community acquired pneumonia and as differantial diagnosis of D-dimer in pulmonary embolism and pneumonia [dissertation]. Bursa: Uludağ University; 2006.

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RESEARCH ARTICLE

An investigation of the role of trace elements and biochemical parameters in patients with COVID-19

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ABSTRACT

Aim: The COVID-19 pandemic is an emergent viral respiratory disease characterized by high fever and shortness of breath, and it was declared a pandemic by the World Health Organization in March 2020. Early assessment of patients' biochemical tests is important for accelerating diagnosis, allowing effective treatment, and controlling the further spread of the disease. The present study aimed to investigate the association between the disease, trace elements -including copper (Cu), zinc (Zn), selenium (Se), manganese (Mn), and cobalt (Co) vitamin D, Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) biochemical levels, and the correlation between the parameters tested in patients with COVID-19.

Methods: In our study, 40 patients (case group) who were hospitalized with a diagnosis of COVID-19 based on chest X-ray images and RT-PCR results evaluated by an infectious diseases specialist were included, along with 40 healthy individuals (control group) over the age of 18 who had no prior symptoms of COVID-19, no visits to a medical doctor for COVID-19, and no history of hospitalization due to the disease. Beckman Coulter AU5800 (Beckman Coulter, Brea, CA, USA) autoanalyzer was used for spectrophotometric analyses of clinical biochemistry tests, and vitamin D levels were examined using the HPLC method with the Shimadzu SIL-20A HT autosampler. Levels of trace elements-including Cu, Zn, Se, Mn, and Co-were measured by inductively coupled plasma mass spectrometry (ICP-MS) on an ICP-MS Bruker Aurora M90 analytical complex. The normal distribution hypothesis for the variables in question was tested using the Kolmogorov–Smirnov test. Student's t-test was used for intergroup comparisons of variables meeting the normal distribution hypothesis, whereas Mann–Whitney U test was used for variables that did not meet the hypothesis.

Results: Vitamin D levels were much lower in the case group (12.05 ng/mL ± 6.27) compared to the control group (23.54 ng/mL ± 10.54), and the difference was statistically significant ($p < 0.001$). Serum Cu, Zn, Se, Mn, and Co levels in the

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control group were higher compared to the COVID-19 group, yet only the differences in Zn, Se, and Mn levels were statistically significant ($p < 0.05$, $p < 0.001$, $p < 0.05$, respectively).

Conclusion: Decreased levels of vitamin D and trace elements (Se, Zn, Mg and Cu) are associated with the development of viral pathogens, including COVID-19, as well as increased ALT and AST parameters. It was concluded that a diet rich in vitamins and trace elements would strengthen the immune system, reduce the rate of virus spread, and slow down the disease aggravation.

Keywords: Clinical chemistry tests, COVID-19, vitamin D, trace elements

INTRODUCTION

The disease, which has caused severe mortality and morbidity rates across the world due to SARS-CoV-2-a member of the betacoronavirus family with an enveloped, positive single-stranded RNA genome-was named COVID-19 by the WHO (1). COVID-19 infection, a global pandemic that has caused more than one million deaths, is characterized by a wide range of symptoms, from asymptomatic to fatal (2,3). The disease is either asymptomatic or presents with symptoms such as fatigue, headache, joint and muscle pain, loss of smell, nasal congestion, nausea and vomiting, anorexia and diarrhea. These symptoms are present in more than 80% of patients diagnosed with COVID-19, while the remainder may present with more severe or critical symptoms (1,4-6). Furthermore, actively circulating macrophages can attack vital organs, including the lungs, liver, and brain, leading to ARDS (Acute Respiratory Distress Syndrome) and death (7). In general, a range of viral and bacterial infections induce cytokine production, inflammation, an increase in free radicals, and a depletion of antioxidants upon triggering oxidative stress (5,6,8). Lipid peroxides and free oxygen radicals, formed through the oxidation of unsaturated fatty acids or other lipids, may lead to cell membrane damage and loss of function. Consequently, this may cause cell mutations, weaken the immune system, and even necrosis by damaging DNA (9-11).

In cases of infection, particularly COVID-19, nutritional support should include supplementation with vitamins, trace elements; copper (Cu), zinc (Zn), selenium (Se), manganese (Mn), iron (Fe), and magnesium (Mg) as well as carotenoids and polyphenols, with the aim of strengthening the immune system and reducing inflammation (1,5,12). Cu, Zn, Se, and Mg are the most important trace elements due to their immunomodulatory and antiviral properties (1,6,10,12). Many reactive oxygen species are produced during viral infections, and important antioxidant enzymes are used to reduce them as a part of the free radical defense mechanism. Cu and Zn are cofactors of one of these enzymes, i.e., superoxide dismutase (SOD), and Se acts as a cofactor for the GSH-Px enzyme (10,13). Zn is considered the second most important trace element in the cell after iron and it is an anti-inflammatory agent that reduces the production of oxidative stress biomarkers (10,14). Deficiency of Zn may lead to immunodeficiency by promoting mechanisms such as lymphopenia and increased apoptosis of lymphocytes. (10,14). Cu is associated with immunity to viral infections and the function of Natural Killer cells (NK) and T helper (Th) cells, and its deficiency is associated with decreased interleukin-2 (IL-2) levels (13). A decrease in serum Zn levels has been reported to correlate with increased severity of COVID-19, along with an increase in the Cu/Zn ratio (15). Se is a component of selenoproteins, which are important for the immune and antioxidant systems, and also contain selenocysteine amino acid in their active sites (12,16). Se plays an immunoregulatory role and is involved both structurally and as a cofactor in the regulation of endocrine functions during inflammatory processes. It is an important cofactor of GSH-Px, which suppresses oxidative stress in the systemic inflammatory response. Furthermore, Se increases phagocyte and NK cell activity, T cell proliferation, and immunoglobulin synthesis (17). Selenium deficiency is a known risk factor for viral infections and has also been reported as a contributing factor to mortality in severe conditions such as sepsis and polytraumatic injuries (12). Vitamin D regulates both the innate and acquired immune systems by affecting the proliferation and phenotype of T cells (18,19).

An investigation of trace elements, vitamins, and biochemical parameters in patients with COVID-19 could contribute to more robust and comprehensive interventions in the fight against this disease and other viral infections. The present study aimed to investigate the association between the disease and trace elements (including Cu, Zn, Se, Mn, and Co), vitamin D, Alanin Aminotransferaz (ALT) and Aspartat Aminotransferaz (AST) levels, and the correlation between the parameters tested in patients with COVID-19.

MATERIALS AND METHODS

The study included 40 patients (case group) who presented to Dicle University Faculty of Medicine Hospital with COVID-19 symptoms, were diagnosed with COVID-19 based on the *Public Health Surveillance for COVID-19: interim guidance* by WHO, and were hospitalized by an infectious diseases specialist as a result of positive RT-PCR test on the samples collected by nasopharyngeal swab and lung X-ray images. The study also included 40 healthy individuals (control group) over the age of 18 who had no COVID-19 symptoms, had not visited a doctor, or had no history of hospitalization due to COVID-19. The study was approved by the Ministry of Health of the Republic of Turkey (2021-03-30T19_52_07) and the Ethics Committee of Dicle University Faculty of Medicine (No: 20/08/2021-372). Patients who were diagnosed with SARS-CoV-2 infection, but had no viral RNA as indicated by the RT-PCR test results were excluded from the study. Patients under the age of 18, as well as those with chronic diseases (e.g., diabetes mellitus, hypertension, coronary heart disease, chronic kidney disease, chronic lung disease, neoplasia), and pregnant or breastfeeding women were excluded from the study.

Spectrophotometric analyses of clinical biochemistry tests were performed, hemogram measurements were conducted using a SYSMEX XN-1000 (Sysmex, Kobe, Japan) hematology analyzer, and vitamin D levels were determined by HPLC using a Shimadzu SIL-20A HT autosampler. For the Cu, Zn, Se, Mn, Co, ALT, and AST tests, blood samples were collected into standard clinical biochemistry test tubes, centrifuged at 1500 g for 20 minutes, and the resulting sera were then separated and stored at –80°C.

After the sera were brought to room temperature and thawed on the day of analysis, serum levels of trace elements Cu, Zn, Se, Mn, and Co were measured by ICP-MS on ICP-MS Bruker Aurora M90 analytical complex. ICP-MS (Agilent, Thermo Scientific, Perkin Elmer, Bruker Daltonics, Germany), Solutions; Merck, Israel.

ALT and AST levels were analyzed using the Beckman AU5800 ISE analyzer (20). The selected AU5800 features single or dual ISE flow cells in clinical chemistry module configurations (21). Vitamin D analysis was performed using an HPLC device manufactured by Shimadzu (Kyoto, Japan) (22).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) for Windows was used for statistical analyses of the data obtained in the study. The study data were expressed in percentages (%), mean ± standard deviation (SD), mean, median, and correlation coefficient (r).

The normal distribution hypothesis was tested using the Kolmogorov–Smirnov test for the variables in question. Mean and SD were used for variables that met the normal distribution hypothesis. For the comparison between groups, Student's t-test was used for variables that met the assumption of normal distribution, while the Mann–Whitney U test was applied to those that did not. Chi-squared test was used to compare categorical variables, and the relationship between numerical variables was investigated by Spearman's correlation analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

The study group consisted of 40 patients (25 females and 15 males) with COVID-19. The mean age of the patients was 57.75 ± 19.85 years. The control group included 40 healthy individuals (28 females and 12

Table 1. Age, gender and biochemistry test results of groups				
		Control (N: 40)	**Patients (N: 40)**	**p**
Gender (n)	Female	28	25	0.001***
	Male	12	15	
Age (years) median (IQR)		33 (12.75)	55.5 (37.75)	0.001***
ALT U/L median (IQR)		21.78 (10.43)	28.60 (32.32)	0.137
AST U/L median (IQR)		23 (9.84)	29.6 (21.15)	0.017*
D Vit (ng/mL)		23.54±10.54	12.05±6.27	0.001***

Data are presented as mean ± SD or n (%), median, IQR. *p < 0.05 vs. controls. **p < 0.01 vs. controls. *** p < 0.001. Vit D: Vitamin D, P: Phosphorus, Mg: Magnesium, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, IQR: Interquartile Range.

Table 2. Serum trace element levels of groups			
	Control (N: 40)	**Patients (N: 40)**	**p**
Co median (IQR), (µg/L)	27.08 (16.38)	17.96 (19.19)	0.14
Cu median (IQR), (µg/L)	1328.10 (704.87)	1302.26 (751.80)	0,288
Zn median (IQR), (µg/L)	1675.25 (276.90)	1440.77 (508.84)	0.001***
Se (µg/L)	108.30±42,11	64.59±24.29	0.001***
Mn median (IQR), (µg/L)	18.81 (5.68)	11.32 (4.47)	0.001***
Cu/Zn median (IQR)	0.84 (0.37)	1.04 (0.63)	0.094

Data are presented as mean ± SD or n (%), median, IQR. *p < 0.05 vs. controls. **p < 0.01 vs. controls. *** p < 0.001. Co: Cobalt, Cu: Copper, Zn: Zinc, Se: Selenium, Mn: Manganese, IQR: Interquartile Range.

males) with a mean age of 35.02 ± 8.12 years. The patient group was composed of older individuals, and there was a statistically significant difference in age between the two groups (There were more female patients than male patients; p<0.001) (Table 1).

As presented in Table 1, serum vitamin D levels were significantly lower in the COVID-19 group (12.05 ± 6.27 ng/mL) compared to the control group (23.54 ± 10.54 ng/mL), with the difference being statistically significant (p < 0.001).

Serum Cu, Zn, Se, Mn, Co levels are presented in Table 2. Serum Cu, Zn, Se, Mn, and Co levels in the control group were higher compared to the COVID-19 group, yet only the differences in Zn, Se, and Mn levels were statistically significant (p < 0.05, p < 0.001, p < 0.05, respectively) (Table 2). No statistically significant difference was found between the patient and control groups in terms of ALT enzyme levels (p>0.05). A significant difference was found in terms of AST enzyme levels (p<0.05) (Table 1). Serum AST level was higher in patient group.

DISCUSSION

This study demonstrates a significant association between COVID-19 and reduced serum levels of vitamin D, Zn, Se, and Mn. These micronutrients are known to play essential roles in immune regulation, antioxidant defense, and inflammatory responses. The observed deficiencies in the case group may contribute to increased vulnerability to SARS-CoV-2 infection or to the progression of the disease. Notably, the markedly lower levels of vitamin D in COVID-19 patients support previous findings suggesting its potential role in modulating respiratory infections and immune response. Trace elements, including Zn, Mn, Se, and Cu, help reinforce the immune system, support the immune system, and are also involved in the composition of various viral enzymes, proteases, and polymerases that help prevent viral infection

(23). Both Zn and Cu are trace elements with antiviral activity that activate the immune system. Al-Saleh et al. reported Zn deficiency (<0.693 µg/mL) in 25% of patients with COVID-19, whereas only 3% had Cu deficiency (<0.18 µg/mL), and 28% had elevated Cu levels (>1.401 µg/mL). Nevertheless, although a significant amount of patients in the aforementioned study had Zn deficiency, the authors did not identify a correlation between this deficiency and severity of COVID-19. Patients who died from COVID-19 had lower serum Zn levels (0.7 µg/mL) compared to the survivors (1.117 µg/mL), but the difference was merely on the borderline of statistical significance ($p = 0.065$) (1).

Muhammad et al. reported that serum Mn, Zn, Cu, and Se levels were significantly lower in COVID-19 patients compared to controls (23). Typically, the Cu/Zn ratio is close to 1:1 (24) and it has been suggested that Cu/Zn >2 indicated severe bacterial infection (25). Al-Saleh et al. reported a high Cu/Zn ratio (1.5 ± 0.63) in their study. They identified 128 patients (~83%) with a Cu/Zn ratio of >1 and 33 patients (21%) with a Cu/Zn ratio of >2, and suggested that an elevated Cu/Zn ratio may exacerbate inflammation in COVID-19 patients and might be associated with the severity of disease (1).

Skalny et al. categorized COVID-19 patients into mild, moderate, and severe groups, and reported that decreased levels of Zn, Mn, and Cu, as well as an increased Cu/Zn ratio, were particularly observed in the severe group. Especially in the moderate and severe groups, Zn values were significantly lower compared to the mild disease group and healthy controls. The Cu/Zn ratio gradually increased in COVID-19 patients (for mild, moderate, and severe disease cases: 18%, 39%, and 39%, respectively), and elevations in Cu levels and the Cu/Zn ratio were closely correlated with markers of disease severity (15). In the present study, only the difference in Zn levels was statistically significant despite the fact that both Cu and Zn levels were lower in the patient group compared to controls. The Cu/Zn ratio was >1 (1.04) in the patient group.

Selenium is reportedly important for the maturation and function of CD8+ T cells and NK cells, and it plays a prominent role in the production of antibodies (6,26,27). A German study found that the serum Se levels in surviving COVID-19 patients were significantly higher compared to the deceased patients (12). In China, it was reported that Se levels were significantly correlated with the recovery rate in patients with COVID-19, and patients with higher Se concentrations maintained a higher rate of recovery (26). Similarly, Im et al. identified Se deficiency in 42% of COVID-19 patients in their study conducted in Korea (28). In the study of Skalny et al., serum Se levels were lower in COVID-19 patients compared to healthy individuals (15). Consistent with the results of previous studies, the Se levels in the present study were lower in the COVID-19 group compared to healthy controls ($p<0.001$).

Mn has been reported to play an important role in innate immunity and antiviral defense, and that Mn, Fe, or Zn deficiency have been associated with increased incidence of infectious disease and higher mortality rates. A Chinese study by Zeng et al. reported decreased Mg and Mn levels in patients with COVID-19 through whole blood testing, and noted significant differences between severe disease and non-severe disease groups in this regard ($p < 0.05$) (29). A study by Muhammad et al. found that Mn levels were lower in patients with COVID-19, contrary to the elevated Mn levels reported by the study of Skalny et al. (15). Additionally, a study conducted in Kazakhstan observed a decrease in Mn concentrations ($p <0.001$) upon trace element analysis of hair strands of those who recovered from COVID-19 (30). In the present study, Mn levels were lower in the COVID-19 group ($p < 0.001$).

Zinc induces regulatory T cells (TREGs) and suppresses proinflammatory TH17 and TH9 cell differentiation. Zinc supplementation was recommended as part of a potential solution to immunosuppression, since zinc deficiency is associated with impaired immune function and an increased risk of infection (31). Zinc inhibits the replication of various RNA viruses, including SARS-CoV-2. Considering the inhibitory effect of zinc on the replication of coronavirus, zinc would likely have similar effects on COVID-19 infection (32). In the present study, a significant difference in zinc trace element levels was detected between the patient group and control group, with zinc levels being significantly lower in the patient group ($p < 0.001$).

A study by Polat et al., reported that aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), laktat dehidrogenaz (LDH), Gama-glutamil transferaz (GGT), Alkalen fosfataz (ALP) levels, which are indicators of liver, and heart functions, were significantly higher in the COVID-19 group (33). In the present study, ALT and AST levels were higher in the COVID-19 group, consistent with the study by Polat et al. ($p < 0.05$).

Vitamin D contributes to the production of antimicrobial peptides against bacteria, viruses, and fungi by stimulating the immune system. Vitamin D has notable effects on the immune system along with one of its functions, i.e., regulating calcium and phosphorus homeostasis (26). An increasing number of studies suggest that vitamin D deficiency is associated with a higher risk of contracting various infectious diseases (including respiratory viruses) and with worse clinical outcomes due to the loss of its immunomodulatory effects (34). Povaliaeva et al. suggested that their study results were consistent with the overall low prevalence of vitamin D levels, noting that only 3% of patients with COVID-19 had adequate vitamin D levels, while the median 25OH-D3 level in patients with COVID-19 was only 10.8 ng/mL (18). A meta-analysis of the correlation between 25-hydroxyvitamin-D [25(OH) D] levels and the risk and outcomes of COVID-19 reported that the risk of COVID-19 was higher in cases of vitamin D deficiency, and that there was a significant relationship between vitamin D deficiency and the severity of disease and mortality (35). One study found that 68% of COVID-19 patients had vitamin D-3 deficiency. However, there was no significant difference in vitamin D-3 deficiency between patients with mild, moderate, and severe symptoms, and asymptomatic patients, because vitamin D deficiency was present in all subgroups. An Israeli study reported that 25(OH)D deficiency (≤20 ng/mL) approximately doubled the risk of hospitalization due to COVID-19 infection (36). In the present study, vitamin D levels were lower in patients with COVID-19, consistent with findings in other studies ($p < 0.001$).

The present study found that Cu, Zn, Mn, and Se levels, which had a well-established role in reinforcing the immune system, were lower in patients with COVID-19 compared to the control group. Oxidative stress appears to be elevated in patients with COVID-19, leading to increased antioxidant utilization and consequently reduced serum levels of trace elements. The main limitation to the present study is that it was designed as a single-center research and the sample size was relatively small. Therefore, the results cannot be generalized. Furthermore, most of the hospitalized patients were elderly individuals, and demographic data with adequate details pertaining to the patient and control groups could not be obtained because the epidemic period was very busy for hospital staff.

CONCLUSION

In light of the present study and previous reports, vitamin (vitamins A, C, D and E) and trace element (Se, Zn and Cu) deficiencies, which are associated with weakened immune system, may contribute to viral diseases, including COVID-19, and aggravate the disease by increasing ALT and AST levels, which are indicators of hepatocellular injury.

It was concluded that a diet rich in vitamins and trace elements may strengthen the immune system, reduce the rate of virus spread, and slow down the disease aggravation. We believe that the present study will guide physicians by showing the importance of nutrition in all viral diseases, especially COVID-19, and serve as a guide for future, more comprehensive studies.

Ethical approval

This study has been approved by the Dicle University Medical Faculty Ethics Committee For Non-Interventional Studies (approval date 20/08/2021, number 372). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: HT; Concept: İS, VU, RECE; Design: İS, VU, RECE; Data Collection or Processing: İS, VU, RECE; Analysis or Interpretation: İS, VU, RECE; Literature Search: EÖ, ÇM; Writing: İS, VU, RECE, EÖ, ÇM, HT. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Al-Saleh I, Alrushud N, Alnuwaysir H, et al. Essential metals, vitamins and antioxidant enzyme activities in COVID-19 patients and their potential associations with the disease severity. Biometals. 2022; 35(1): 125-45. [Crossref]
2. Doğan S, Bal T, Çabalak M, Dikmen N, Yaqoobi H, Ozcan O. Oxidative stress index can be a new marker related to disease severity in COVID-19. Turkish Journal of Biochemistry. 2021; 46: 349-57. [Crossref]
3. World Health Organization (WHO). COVID-19 cases | WHO COVID-19 dashboard. Available at: https://data.who.int/dashboards/covid19/cases
4. Saja RK, Al-Mamouri Ali MA, Al-Kufaishi. Evaluation of total antioxidant capacity and total oxidant status in patients with COVID-19. J Pharm Negat Results. 2022; 13(4): 125-9. [Crossref]
5. Karkhanei B, Talebi Ghane E, Mehri F. Evaluation of oxidative stress level: total antioxidant capacity, total oxidant status and glutathione activity in patients with COVID-19. New Microbes New Infect. 2021; 42: 100897. [Crossref]
6. Shakoor H, Feehan J, Al Dhaheri AS, et al. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? Maturitas. 2021; 143: 1-9. [Crossref]
7. Andreou A, Trantza S, Filippou D, Sipsas N, Tsiodras S. COVID-19: the potential role of copper and N-acetylcysteine (NAC) in a combination of candidate antiviral treatments against SARS-CoV-2. In Vivo. 2020; 34(Suppl 3): 1567-88. [Crossref]
8. Ntyonga-Pono MP. COVID-19 infection and oxidative stress: an under-explored approach for prevention and treatment? Pan Afr Med J. 2020; 35(Suppl 2): 12. [Crossref]
9. Bagher Pour O, Yahyavi Y, Karimi A, et al. Serum trace elements levels and clinical outcomes among Iranian COVID-19 patients. Int J Infect Dis. 2021; 111: 164-8. [Crossref]
10. Bayraktar N, Bayraktar M, Ozturk A, Ibrahim B. Evaluation of the relationship between aquaporin-1, hepcidin, zinc, copper, and iron levels and oxidative stress in the serum of critically ill patients with COVID-19. Biol Trace Elem Res. 2022; 200(12): 5013-21. [Crossref]
11. Martín-Fernández M, Aller R, Heredia-Rodríguez M, et al. Lipid peroxidation as a hallmark of severity in COVID-19 patients. Redox Biol. 2021; 48: 102181. [Crossref]
12. Moghaddam A, Heller RA, Sun Q, et al. Selenium deficiency is associated with mortality risk from COVID-19. Nutrients. 2020; 12(7): 2098. [Crossref]
13. Nedjimi B. Can trace element supplementations (Cu, Se, and Zn) enhance human immunity against COVID-19 and its new variants? Beni Suef Univ J Basic Appl Sci. 2021; 10(1): 33. [Crossref]
14. Joachimiak MP. Zinc against COVID-19? Symptom surveillance and deficiency risk groups. PLoS Negl Trop Dis. 2021; 15(1): e0008895. [Crossref]
15. Skalny AV, Timashev PS, Aschner M, et al. Serum zinc, copper, and other biometals are associated with COVID-19 severity markers. Metabolites. 2021; 11(4): 244. [Crossref]
16. Alexander J, Tinkov A, Strand TA, Alehagen U, Skalny A, Aaseth J. Early nutritional interventions with zinc, selenium and vitamin d for raising anti-viral resistance against progressive COVID-19. Nutrients. 2020; 12(8): 2358. [Crossref]
17. Tek NA, Koçak T. Koronavirüsle (COVID-19) mücadelede beslenmenin bağışıklık sisteminin desteklenmesinde rolü. Gazi Sağlık Bilimleri Dergisi. 2020; Özel Sayı: 18-45.
18. Povaliaeva A, Bogdanov V, Pigarova E, et al. Impaired vitamin D metabolism in hospitalized COVID-19 patients. Pharmaceuticals (Basel). 2022; 15(8): 906. [Crossref]
19. Davoudi A, Najafi N, Aarabi M, et al. Lack of association between vitamin D insufficiency and clinical outcomes of patients with COVID-19 infection. BMC Infect Dis. 2021; 21(1): 450. [Crossref]
20. Tietz NW, Pruden EL, Siggaard-Anderson O. Electrolytes. In: Teitz NW, editor. Fundamentals of clinical chemistry. 3nd ed. Philadelphia: WB Saunders Company; 1987: 614-24.
21. Jia KK, Zhang J. Evaluation of five routine glucose methods on an Olympus AU5400 analyzer using the CDC hexokinase reference method. Clin Chem Lab Med. 2010; 48(3): 361-4. [Crossref]
22. Keyfi F, Nahid S, Mokhtariye A, Nayerabadi S, Alaei A, Varasteh A-R. Evaluation of 25-OH vitamin D by high performance liquid chromatography: validation and comparison with electrochemiluminescence. J Anal Sci Technol. 2018; 9: 25. [Crossref]
23. Muhammad Y, Kani YA, Iliya S, et al. Deficiency of antioxidants and increased oxidative stress in COVID-19 patients: a cross-sectional comparative study in Jigawa, Northwestern Nigeria. SAGE Open Med. 2021; 9: 2050312121991246. [Crossref]
24. Malavolta M, Piacenza F, Basso A, Giacconi R, Costarelli L, Mocchegiani E. Serum copper to zinc ratio: relationship with aging and health status. Mech Ageing Dev. 2015; 151: 93-100. [Crossref]
25. Bahi GA, Boyvin L, Méité S, et al. Assessments of serum copper and zinc concentration, and the Cu/Zn ratio determination in patients with multidrug resistant pulmonary tuberculosis (MDR-TB) in Côte d'Ivoire. BMC Infect Dis. 2017; 17(1): 257. [Crossref]

26. Bae M, Kim H. Mini-review on the roles of vitamin C, vitamin D, and selenium in the immune system against COVID-19. Molecules. 2020; 25(22): 5346. [Crossref]

27. Domingo JL, Marquès M. The effects of some essential and toxic metals/metalloids in COVID-19: a review. Food Chem Toxicol. 2021; 152: 112161. [Crossref]

28. Im JH, Je YS, Baek J, Chung MH, Kwon HY, Lee JS. Nutritional status of patients with COVID-19. Int J Infect Dis. 2020; 100: 390-3. [Crossref]

29. Zeng HL, Yang Q, Yuan P, Wang X, Cheng L. Associations of essential and toxic metals/metalloids in whole blood with both disease severity and mortality in patients with COVID-19. FASEB J. 2021; 35(3): e21392. [Crossref]

30. Batyrova G, Tlegenova Z, Kononets V, et al. Content of essential trace elements in the hair of residents of the Caspian Region of the Republic of Kazakhstan who recovered from COVID-19. Diagnostics (Basel). 2022; 12(11): 2734. [Crossref]

31. Yaghoubi N, Youssefi M, Jabbari Azad F, Farzad F, Yavari Z, Zahedi Avval F. Total antioxidant capacity as a marker of severity of COVID-19 infection: possible prognostic and therapeutic clinical application. J Med Virol. 2022; 94(4): 1558-65. [Crossref]

32. Mehri F, Rahbar AH, Ghane ET, Souri B, Esfahani M. Changes in oxidative markers in COVID-19 patients. Arch Med Res. 2021; 52(8): 843-9. [Crossref]

33. Lambadiari V, Mitrakou A, Kountouri A, et al. Association of COVID-19 with impaired endothelial glycocalyx, vascular function and myocardial deformation 4 months after infection. Eur J Heart Fail. 2021; 23(11): 1916-26. [Crossref]

34. Watkins RR, Lemonovich TL, Salata RA. An update on the association of vitamin D deficiency with common infectious diseases. Can J Physiol Pharmacol. 2015; 93(5): 363-8. [Crossref]

35. Kazemi A, Mohammadi V, Aghababaee SK, Golzarand M, Clark CCT, Babajafari S. Association of vitamin D status with SARS-CoV-2 infection or COVID-19 severity: a systematic review and meta-analysis. Adv Nutr. 2021; 12(5): 1636-58. [Crossref]

36. Merzon E, Tworowski D, Gorohovski A, et al. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. FEBS J. 2020; 287(17): 3693-702. [Crossref]

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RESEARCH ARTICLE

Factors affecting mortality in patients with *Klebsiella pneumoniae* bloodstream infection in the intensive care unit

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ABSTRACT

Aim: In recent years, *Klebsiella pneumoniae* bloodstream infections (KP-BSIs) have emerged as a major public health concern due to their increasing prevalence and their strong association with high morbidity and mortality rates. Despite this growing threat, there is a lack of epidemiological data specific to Bolu province, Turkey. This study aims to characterize the epidemiological, microbiological, and clinical features of KP-BSIs in this region, with a particular focus on identifying risk factors associated with carbapenem resistance and patient mortality.

Methods: A total of 142 patients with KP-BSIs that developed in the intensive care unit (ICU) over approximately four years were included in the study. The association between demographic and clinical data of the patients and carbapenem resistance and mortality was analyzed.

Results: Among the patients monitored in the intensive care unit, 64.8% died. No independent predictors were identified for the development of carbapenem-resistant *K. pneumoniae* infections in the multivariate analysis. However, the following factors were found to be associated with an increased risk of mortality: age over 65 years, the presence of pneumonia or a urinary tract infection a bloodstream infection linked to an intravenous catheter, prior use of a central venous catheter, hospitalisation within the last three months, recent or prolonged exposure to broad-spectrum antibiotics, and infections at other anatomical sites. Notably, having a tracheostomy was associated with a reduced risk of death, while a one-unit increase in albumin was associated with a 13.8% lower risk of death, a one-unit increase in C-reactive protein (CRP) was associated with a 1.9% higher risk.

Conclusions: This study provides important data on the rate of KP-BSI isolated from secondary care facilities and the risk factors for mortality. Existing literature has typically focused on identifying risk factors for death in tertiary care public hospitals. However, this study examined the intensive care units of secondary care public hospitals and found high mortality rates among patients. The high mortality rate of patients with KP-BSI highlights the urgency of implementing appropriate infection control strategies.

Keywords: *Klebsiella pneumoniae*, bloodstream infection, mortality

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INTRODUCTION

The marked increase in antibiotic resistance in *K. pneumoniae* isolates has been linked to fatal outcomes. Firstly, it has been demonstrated that bloodstream infections (BSIs) caused by extended-spectrum β-lactamase (ESBL) *Enterobacterales* are associated with treatment failure (1-3). More recently, BSIs caused by carbapenem-resistant *K. pneumoniae* (CRKP) were reported to result in mortality in approximately 49%-57% of cases (4-6).

The most common risk factors for mortality in patients with BSI caused by *K. pneumoniae* are the severity of the underlying disease, length of time in the intensive care unit (ICU) at the onset of infection, presence of ESBL or CRKP strains, and delay in initiating appropriate therapy. Conversely, controlling the source of infection and administration of early and appropriate antimicrobial therapy have been associated with improved survival (7). Therefore, it is useful to assess the risk of CRKP in patients with suspected *Klebsiella pneumoniae* bloodstream infections (KP-BSI) and to examine risk factors for mortality.

MATERIALS AND METHODS

Ethical approval

The study received ethics committee approval from the Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (decision no: 201 /date: September 10, 2024). All procedures were performed in accordance with the ethical standards set by the Declaration of Helsinki.

Bacterial isolates, identification, susceptibility testing, and study design

A total of 142 non-duplicate clinical *K. pneumoniae* isolates (one isolate per patient) were included in the study. These isolates were obtained from blood cultures in the ICU of Bolu State Hospital between January 2021 and August 2024, and they were accepted as causative agents. All strains isolated during the study period were selected for inclusion in the study.

A retrospective, patient- and laboratory-based surveillance approach was used to analyze the data obtained from relevant sources. Adult patients (18 years of age or older) who had started antibacterial treatment for the infectious agent in question and whose blood samples collected 48 hours after admission to the ICU showed growth of *K. pneumoniae* were included in the study. Blood samples were taken into blood culture bottles and incubated in an automated system. After the preliminary identification of the samples that showed growth within five days, they were transferred to 5% sheep blood agar and EMB agar media and incubated at 35.5-37°C for 18-24 hours. Antimicrobial identification and antibiotic susceptibility testing of the isolates were performed using standard conventional methods with a fully automated device (VITEK2, bioMerieux, France). EUCAST methods and interpretation criteria were used for all antimicrobial agents (8).

Age, sex, clinical data, prognosis (mortality or survival), and laboratory parameters—including albumin, glucose, creatinine, procalcitonin, C-reactive protein (CRP), hemoglobin, white blood cell count (WBC), and lymphocyte count (LYM)—were recorded following retrieval from the institutional database and patient files.

Clinical data included hospitalization within the past three months, broad-spectrum antibiotic use, antibiotic use for ≥5 days within the past three months, comorbidities, possible sources and risk factors for bacteremia, and 28-day mortality.

Statistical analysis

The research data were analzed using the IBM SPSS 26.0 program. Descriptive statistics were presented for categorical variables as numbers and percentages, and for interval variables as mean and standard deviation. A Chi-square test was employed to compare categorical variables in independent groups. A Student's t-test was used to compare interval variables with a normal distribution between two independent groups. In the multivariate analysis, variables with $p<0.05$ in univariate analysis were added to the logistic

regression model, and the enter method was used. The statistical significance level was set at p<0.05.

RESULTS

The study included 142 patients with BSIs associated with *K. pneumoniae* in the anaesthesia ICU of a public hospital. The majority of patients were male (54.9%) and 65 years of age or older (80.3%). The most common infections were sepsis (95.8%), pneumonia (74.6%), and urinary tract infections (61.3%). The most common comorbidities were hypertension (47.2%), diabetes (29.6%), and heart disease (23.9%). The most common invasive devices were urinary catheters (95.1%) and central venous catheters (71.8%). A total of 62.7% of patients had a history of hospitalisation within the previous three months, 62% had used broad-spectrum antibiotics for more than five days or within the last three months, and 79.6% had concomitant infection growth in another site.

Carbapenem-susceptible and carbapenem-resistant organisms represented 14.1% and 85.9% of patients, respectively. There was no statistically significant difference between age, sex, focus of infection, concomitant diseases, use of invasive devices, hospitalisation wtihin the last three months, history of antibiotic use, growth in another focus and laboratory parameters of carbapenem-sensitive and resistant patients (p>0.05) (Table 1).

Risk factors for mortality

While 35.2 percent of the patients survived, 64.8 percent died within 28 days. The univariate analysis identified the following risk factors for death: age 65 years or older [OR: 3.793 (1.606-8.961)], pneumonia [OR: 1.894 (0.516-6.949)], urinary tract infection [OR: 2.067 (1.021-4.184)] and BSI associated with an intravenous catheter [(OR: 4.634 (1.308-16)]. The following factors were identified as risk factors for death in univariate analysis: age over 65 years [OR: 3.793 (1.606-8.961)], pneumonia [OR: 1.894 (0.516-6.949)], urinary tract infection [OR: 2.067 (1.021-4.184)], BSI associated with an intravenous catheter [OR: 4.634 (1.308-16.577)], history of central venous catheter [OR: 3.511 (1.050-11.738)], history of hospitalisation in the last three months [OR: 1.270 (0.148-10.934)], history of broad-spectrum antibiotic use for more than five days or within the last three months [OR: 1.067 (0.134-8.486)], and the presence of an accompanying growth in another focus [OR: 4.142 (1.762-9.734)]. It was established that the presence of a tracheostomy was associated with a reduced risk (OR: 0.128, 95% CI: 0.032-0.519). When examining the correlation between a one-unit increase in laboratory parameters and the risk of death, the following results were observed: WBC (OR: 1.082, 1.017-1.151), glucose [OR: 1.008 (1.001–1.016)], creatinine (OR: 3.110, 1.593-6.071), and procalcitonin (OR: 1.039, 1.003-1). Elevated levels of CRP [OR: 1.031 (1.019-1.044)] and other parameters, including WBC [OR: 1.082 (1.017-1.151)], glucose [OR: 1.008 (1.001-1.016)], creatinine [OR: 3.110 (1.593-6.071)], procalcitonin [OR: 1.039 (1.003-1.077)], and CRP [OR: 1.031 (1.019-1.044)] were found to increase the risk of death. Conversely, elevated levels of HGB [OR: 0.758 (0.633-0.908)] and albumin [OR: 0.786 (0.719-0.860)] were associated with a reduced risk of death (Table 2).

The logistic regression analysis, which included variables exhibiting significant differences in the univariate analysis (procalcitonin with a high proportion of missing data was not incorporated into the regression model), revealed that the presence of a central venous catheter was associated with an elevated risk of mortality [OR: 3.511 (1.050-11.738)], whereas the use of a tracheostomy was associated with a reduced risk of mortality [OR: 0.128 (0.032-0.519)]. A one-unit increase in albumin value was associated with a decreased risk of death (OR: 0.862, 95% CI: 0.750–0.991). Conversely, a one-unit increase in CRP value was linked to an increased risk of death (OR: 1.019, 95% CI: 1.001–1.036). The remaining risk factors identified in the univariate analysis did not demonstrate a statistically significant differences in the multivariate analysis (p> 0.05) (Table 3).

Table 1. Comparison of clinical characteristics between carbapenem-resistant *K. pneumoniae* - bloodstream infections (CRKP-BSI) and carbapenem- susceptibility *K. pneumoniae* - bloodstream infection (CSKP-BSI) patients

Demographics		**Total**	**Carbapenem-resistant**		**OR (%95 CI)**	**p value**
			CSKP n=20 (%14.1)	**CRKP n=122 (%85.9)**		
		n (%)	**n (%)**	**n (%)**		
Gender	Male	78 (54.9)	7 (35)	71 (58.2)	ref	0.054
	Female	64 (45.1)	13 (65)	51 (41.8)	0.387 (0.144-1.038)	
Age(y)	< 65 (y)	28 (19.7)	3 (15)	25 (20.5)	ref	0.569
	≥ 65 (y)	114 (80.3)	17 (85)	97 (79.5)	0.685 (0.186-2.522)	
Type of BSI Number of patients						
Sepsis		136 (95.8)	18 (90)	118 (96.7)	3.278 (0.559-19.212)	0.168
Pneumonia		106 (74.6)	11 (55)	95 (77.9)	2.879 (1.081-7.664)	0.030
Urinary system infections		87 (61.3)	13 (65)	74 (60.7)	0.830 (0.309-2.230)	0.713
Bloodstream infections associated with an intravenous catheter		24 (16.9)	1 (5)	23 (18.9)	4.414 (0.562-34.683)	0.127
Surgical site infections		5 (3.5)	0 (0)	5 (4.1)	-	1.000
Complicated skin and soft tissue infections		28 (19.7)	4 (20)	24 (19.7)	0.980 (0.300-3.198)	0.973
Central nervous system infections		2 (1.4)	0 (0)	2 (1.6)	-	1.000
Comorbidities/Underlying disease						
Hypertension		67 (47.2)	8 (40)	59 (48.4)	1.405 (0.537-3.678)	0.489
Coronary artery disease		34 (23.9)	6 (30)	28 (23)	0.695 (0.244-1.977)	0.495
Chronic kidney failure		12 (8.5)	3 (15)	9 (7.4)	0.451 (0.111-1.835)	0.258
Diabetes		42 (29.6)	5 (25)	37 (30.3)	1.306 (0.442-3.858)	0.630
COPD		28 (19.7)	4 (20)	24 (19.7)	0.980 (0.300-3.198)	0.973
Metastatic solid tumor (n=141)		20 (14.2)	1 (5)	19 (15.7)	3.539 (0.447-28.038)	0.205
Neurological		68 (47.9)	11 (55)	57 (46.7)	0.717 (0.277-1.855)	0.494
Surgery		9 (6.3)	2 (10)	7 (5.7)	0.548 (0.105-2.847)	0.470
Risk Factors						
Dialysis		17 (12)	1 (5)	16 (13.1)	2.868 (0.359-22.921)	0.302
Urinary catheter		135 (95.1)	20 (100)	115 (94.3)	-	0.593
Central venous catheter		102 (71.8)	11 (55)	91 (74.6)	2.402 (0.910-6.340)	0.072
Gastrostomy and jejunostomy tube		35 (24.6)	5 (25)	30 (24.6)	0.978 (0.328-2.918)	0.969
Tracheostomy		33 (23.2)	6 (30)	27 (22.1)	0.663 (0.233-1.890)	0.442
Clinical information						
Hospitalization within 3 months		89 (62.7)	15 (75)	74 (60.7)	0.514 (0.175-1.506)	0.221
History of broad-spectrum antibiotic use within 3 months or longer than 5 days		88 (62)	14 (70)	74 (60.7)	0.661 (0.238-1.838)	0.427
Concurrent infectious focus		113 (79.6)	14 (70)	99 (81.1)	1.845 (0.640-5.317)	0.253
Laboratory parameters						
Hemoglobin(g/dL)		9.3±2.1	8.8±2.1	9.4±2.1	1.172 (0.899-1.527)	0.240
White blood cell (10^9/L)		12.8±6.7	12.1±6.7	13.0±6.7	1.020 (0.947-1.100)	0.599
Lymphocyte (10^9/L)		1.2±0.9	0.9±0.8	1.2±1.0	1.591 (0.793-3.193)	0.191
Albümin (g/L)		22.3±5.6	22.7±5.1	22.2±5.7	0.986 (0.904-1.075)	0.749
Glucose (mg/dL)		157.6±64.5	154.1±69.6	158.2±63.9	1.001 (0.993-1.009)	0.791
Creatinine (mg/dL)		1.4±0.9	1.5±1.2	1.4±0.9	0.830 (0.524-1.314)	0.426
Procalcitonin (ug/L) (n=105)		14.3±24.6	21.0±32.6	13.5±23.6	0.990 (0.969-1.011)	0.342
C-reactive protein (mg/L)		107.7±36.9	108.0±39.7	107.7±36.6	1.000 (0.987-1.013)	0.965

COPD: Chronic obstructive pulmonary disease.

Table 2. Comparison of patient mortality according to demographic and clinical characteristics

		Survived n=50 (%35.2)	28-day mortality n=92 (%64.8)	Univariate analysis	
		n (%)	n (%)	OR (%95 CI)	p value
Gender	Male	27 (54)	51 (55.4)	ref	0.870
	Female	23 (46)	41 (44.6)	0.944 (0.473-1.885)	
Age (y)	< 65 (y)	17 (34)	11 (12)	ref	**0.002**
	≥ 65 (y)	33 (66)	81 (88)	3.793 (1.606-8.961)	
Type of BSI number of patients					
Sepsis		44 (88)	92 (100)	-	**0.002**
Pneumonia		32 (64)	74 (80.4)	2.313 (1.067-5.014)	**0.032**
Urinary system infections		25 (50)	62 (67.4)	2.067 (1.021-4.184)	**0.043**
Bloodstream infections associated with an intravenous catheter		3 (6)	21 (22.8)	4.634 (1.308-16.412)	**0.011**
Surgical site infections		1 (2)	4 (4.3)	2.227 (0.242-20.486)	0.470
Complicated skin and soft tissue infections		8 (16)	20 (21.7)	1.458 (0.591-3.601)	0.413
Central nervous system infections		1 (2)	1 (1.1)	0.538 (0.033-8.797)	0.660
Comorbidities/Underlying disease					
Hypertension		18 (36)	49 (53.3)	2.026 (0.998-4.112)	0.050
Coronary artery disease		8 (16)	26 (28.3)	2.068 (0.856-4.995)	0.103
Chronic kidney failure		2 (4)	10 (10.9)	2.927 (0.615-13.920)	0.161
Diabetes		12 (24)	30 (32.6)	1.532 (0.701-3.349)	0.285
COPD		10 (20)	18 (19.6)	0.973 (0.410-2.307)	0.951
Metastatic solid tumor (n=141)		6 (12.2)	14 (15.2)	1.286 (0.461-3.590)	0.631
Neurological		25 (50)	43 (46.7)	0.878 (0.440-1.748)	0.711
Surgery		3 (6)	6 (6.5)	1.093 (0.261-4.571)	0.903
Risk factors					
Dialysis		3 (6)	14 (15.2)	2.812 (0.768-10.302)	0.107
Urinary catheter		45 (90)	90 (97.8)	5.000 (0.933-26.785)	0.060
Central venous catheter		23 (46)	79 (85.9)	7.134 (3.179-16.010)	**<0.001**
Gastrostomy and jejunostomy		13 (26)	22 (23.9)	0.895 (0.405-1.977)	0.784
Tracheostomy		18 (36)	15 (16.3)	0.346 (0.156-0.770)	**0.008**
Clinical information					
Hospitalization within 3 months		24 (48)	65 (70.7)	2.608 (1.278-5.324)	**0.008**
History of broad-spectrum antibiotic use within 3 months or longer than 5 days		22 (44)	66 (71.7)	3.231 (1.573-6.634)	**0.001**
Concurrent infectious focus		32 (64)	81 (88)	4.142 (1.762-9.734)	**0.001**
CRKP		45 (90)	77 (83.7)	0.570 (0.194-1.674)	**0.304**
Laboratory parametres					
Hemoglobin(g/dL)		10.1±2.0	8.9±2.0	0.758 (0.633-0.908)	**0.003**
White blood cell (10^9/L)		10.9±5.4	13.9±7.1	1.082 (1.017-1.151)	**0.013**
Lymphocyte (10^9/L)		1.2±0.7	1.2±1.0	0.930 (0.650-1.331)	**0.692**
Albumin (g/L)		26.0±4.4	20.2±5.2	0.786 (0.719-0.860)	**<0.001**
Glucose (mg/dL)		140.3±38.1	167.0±73.5	1.008 (1.001-1.016)	**0.020**
Creatinine (mg/dL)		1.0±0.5	1.6±1.0	3.110 (1.593-6.071)	**0.001**
Procalcitonin (ug/L) (n=105)		6.2±16.0	18.9±27.3	1.039 (1.003-1.077)	**0.036**
C-reactive protein (mg/L)		84.1±37.0	120.5±30.1	1.031 (1.019-1.044)	**<0.001**

*COPD: Chronic obstructive pulmonary disease.

Table 3. Binary logistic regression analysis for predictors of mortality in patients with *K. pneumoniae* - bloodstream infections

Variables	Multivariate analysis*	
	OR (%95 CI)	p value
Central venous catheter	3.511 (1.050-11.738)	**0.041**
Tracheostomy	0.128 (0.032-0.519)	**0.004**
Albumin (g/L)	0.862 (0.750-0.991)	**0.038**
C-reactive protein (mg/L)	1.019 (1.001-1.036)	**0.035**

*Logistic reggression model-Enter model. Hosmer-Lemeshow test.0.133 Nagerkerke R^2:0.677 Omnibus test:<0.001

DISCUSSION

The results of this retrospective study showed that *K. pneumoniae* infections in the intensive care unit (ICU) are associated with mortality. The following factors were identified as risk factors for mortality: age 65 years or over, pneumonia, urinary tract infection, BSI associated with an intravenous catheter, central venous catheter, history of hospitalisation in the previous three months, history of broad-spectrum antibiotic use for more than five days in the previous three months, and concomitant growth in another focus. Having a tracheostomy was considered a protective factor. Laboratory findings revealed that a one-unit increase in blood albumin decreased the risk of death, whereas a one-unit increase in blood CRP significantly increased the risk of death.

The aim of our study was to determine the relationship between mortality and various risk factors contributing to the development of CRKP during *K. pneumoniae infection episodes* in patients hospitalized in our anesthesia intensive care unit. CRKP infections are a significant public health problem because they can spread rapidly across the globe, have limited treatment options, and negatively impact prognosis. Therefore, early detection of CRKP infections and, thus, reducing the incidence of CRKP are of public health importance (9). While the literature examines risk factors that play important roles in the development of CRKP infection, the reported findings vary widely. Studies have reported that patients with a history of hospitalization, and the use of invasive devices, such as central venous catheters, as well as the use of antibiotics, such as cephalosporins, carbapenems, and quinolones, are risk factors for CRKP. Furthermore, existing literature review also identified steroid use, stem cell transplantation, and an intensive care unit stay as potential risk factors (10,11). In our study, we aimed to identify potential risk factors for the development of CRKP infections. However, despite examining many different variables, we found no independent association between these variables and CRKP infection. One limitation of our study is the small number of patients with CRKP infections in our cohort (14.1%), which may have led to the failure to identify a significant association. However, the presence of multiple patients in the intensive care unit has been suggested as a contributing factor to the spread of CRKP infection. It is also noteworthy that there are studies in the literature consistent with our findings (12).

In our study, the mortality rate was found to be 64.8%, demonstrating the severity of *K. pneumoniae* infections in the intensive care units in Bolu. Therefore, identifying risk factors associated with this mortality rate is crucial for developing effective treatment and improving patient outcomes. In a study by Büyüktuna et al. (13), the mortality rate associated with *K. pneumoniae* infection in a Turkish intensive care unit was reported as 50%. However, in another study by Durdu et al. (14), KP-BSIs were investigated and the mortality rate in intensive care units was determined to be 63.2%. These rates reported in the literature are quite consistent with the findings in our study. Furthermore, Viale et al. (7) conducted a meta-analysis examining publications in MEDLINE between 1977 and 2012, reporting that the mortality rate of KP-BSI ranged from 14% to 46%. Another study conducted in Italy by Delle Rose et al., reported a 67.6% mortality rate for KP-BSI in intensive care units (15).

Thus, although studies on KP-BSI exist in the literature, published findings appear to vary by center. A review by Cekin et al. (16) listed risk factors for mortality, including a diagnosis of sepsis, use of a urinary catheter, a history of surgery, use of broad-spectrum antibiotics, antibiotic-resistant bacteraemia, coronary artery disease, inappropriate empirical treatment, healthcare-associated infections, urinary catheterization, and an ICU stay. In a study conducted in an intensive care unit

in Turkey, Büyüktuna et al. examined *K. pneumoniae* infections and reported that factors such as concurrent chronic obstructive pulmonary disease (COPD), treatment with cephalosporin and colistin antibiotics within the previous three months, and CRKP disease were associated with 20-day mortality (13).

A more detailed investigation of *K. pneumoniae* infections occurring in intensive care units using univariate analysis identified several risk factors. These factors included admission to the intensive care unit, shock, respiratory failure, multiple organ failure, acute renal failure, acidosis, infection due to extensively drug-resistant/pandrug-resistant (XDR/PDR) pathogens and treatment failure (12). A meta-analysis of mortality due to KP-BSIs in the MEDLINE database revealed the highest risk of death was exhibited by elderly patients and those with hematological disease, cirrhosis, solid organ transplantation (SOT), dialysis, heart failure, and critical illness (7). Univariate analysis in our study identified the following as risk factors for mortality: age over 65 years, presence of pneumonia, urinary tract infection, intravenous catheter-related BSI, history of central venous catheter, hospitalisation within the past three months, use of broad-spectrum antibiotics for more than five days within the past three months and presence of concomitant infection growth at another site. The discrepancies in the prevalence of comorbid conditions may be due to the heterogeneous patient profiles observed across different hospitals, as well as varying regional, developmental and socioeconomic factors within countries.

A tracheostomy is a critical procedure frequently performed on patients requiring long-term mechanical ventilation, particularly in emergency situations. The present study demonstrated that tracheostomy was associated with a reduced 28-day mortality risk ([OR: 0.128 (0.032-0.519)]. This finding can be attributed to the benefits of tracheostomy, which facilitate improved airway management and reduce complications associated with long-term intubation, irrespective of the presence of infection. Despite its invasive nature, numerous studies have shown that the timely application of tracheostomy reduces the risk of mortality in critically ill patients (17,18).

In our study, we found that a one-unit increase in CRP increased the risk of death by 1.9% (0.1-3.6) in logistic regression analysis. Studies in the literature have shown that higher CRP concentrations are positively associated with the risk of all-cause mortality in various populations (19). Monitoring CRP levels can provide valuable information about an individual's health status and potential risks. As expected for an acute-phase marker, particularly high CRP levels were more predictive of short-term than long-term mortality (19,20). These results are consistent with our study.

Several studies have consistently shown that low serum albumin levels are associated with an increased risk of mortality. For example, a study published in 2022 found that serum albumin levels (SAL) below 30 g/L were independently associated with a higher risk of both ICU and hospital mortality, even after multivariable adjustment (21). Similarly, a study in 2023 showed that patients with albumin levels below 26 g/L had a significantly increased risk of 90-day and 1-year all-cause mortality (22). The evidence strongly supports the notion that serum albumin levels are a critical factor in predicting mortality risk. Higher albumin levels are associated with reduced mortality, while lower levels increase the risk, particularly in critically ill patients and those with certain medical conditions.

The results of the present study are consistent with previous research, as all identified predictors align with those reported in earlier studies. However, no study was able to correctly associate all predictors. These inconsistencies may be due to the existence of different hospital settings, geographical regions, development levels, and socioeconomic status.

The present study is limited by its single-center design. However, we are confident that the results of our study will provide valuable information for future research. Furthermore, this study provides important data on the rate of KP-BSI isolated from secondary care facilities and the associated risk factors for mortality. Existing literature has typically focused on identifying risk factors for death in tertiary care public hospitals. However, this study examined the intensive

care units of secondary care public hospitals and found high mortality rates among patients. These findings highlight the urgent need for the implementation of appropriate infection control measures for patients with KP-BSI.

CONCLUSIONS

We believe that the identification of risk factors for mortality will contribute to both our hospital database and to the existing literature on KP-BSI. However, it is important to note that our results need to be confirmed by further studies with longer follow-up periods and larger patient populations.

Ethical approval

This study has been approved by the Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (approval date 10/09/2024, number 201).

Author contribution

Concept: ZKC, MD; Design: ZKC; Data Collection or Processing: ZKC, MD; Analysis or Interpretation: ZKC; Literature Search: ZKC, MD; Writing: ZKC. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Rodríguez-Baño J, Pascual A. Clinical significance of extended-spectrum beta-lactamases. Expert Rev Anti Infect Ther. 2008; 6(5): 671-83. [Crossref]
2. Tumbarello M, Spanu T, Di Bidino R, et al. Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. Antimicrob Agents Chemother. 2010; 54(10): 4085-91. [Crossref]
3. Giske CG, Monnet DL, Cars O, Carmeli Y; ReAct-Action on Antibiotic Resistance. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. Antimicrob Agents Chemother. 2008; 52(3): 813-21. [Crossref]
4. Hirsch EB, Tam VH. Detection and treatment options for Klebsiella pneumoniae carbapenemases (KPCs): an emerging cause of multidrug-resistant infection. J Antimicrob Chemother. 2010; 65(6): 1119-25. [Crossref]
5. Tumbarello M, Viale P, Viscoli C, et al. Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae: importance of combination therapy. Clin Infect Dis. 2012; 55(7): 943-50. [Crossref]
6. Qureshi ZA, Paterson DL, Potoski BA, et al. Treatment outcome of bacteremia due to KPC-producing Klebsiella pneumoniae: superiority of combination antimicrobial regimens. Antimicrob Agents Chemother. 2012; 56(4): 2108-13. [Crossref]
7. Viale P, Giannella M, Lewis R, Trecarichi EM, Petrosillo N, Tumbarello M. Predictors of mortality in multidrug-resistant Klebsiella pneumoniae bloodstream infections. Expert Rev Anti Infect Ther. 2013; 11(10): 1053-63. [Crossref]
8. The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Available at: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_14.0_Breakpoint_Tables.xlsx
9. Wang Z, Qin RR, Huang L, Sun LY. Risk Factors for Carbapenem-resistant Klebsiella pneumoniae Infection and Mortality of Klebsiella pneumoniae Infection. Chin Med J (Engl). 2018; 131(1): 56-62. [Crossref]
10. Liu P, Li X, Luo M, et al. Risk Factors for Carbapenem-Resistant Klebsiella pneumoniae Infection: A Meta-Analysis. Microb Drug Resist. 2018; 24(2): 190-8. [Crossref]
11. Li J, Li Y, Song N, Chen Y. Risk factors for carbapenem-resistant Klebsiella pneumoniae infection: A meta-analysis. J Glob Antimicrob Resist. 2020; 21: 306-13. [Crossref]
12. Vardakas KZ, Matthaiou DK, Falagas ME, Antypa E, Koteli A, Antoniadou E. Characteristics, risk factors and outcomes of carbapenem-resistant Klebsiella pneumoniae infections in the intensive care unit. J Infect. 2015; 70(6): 592-9. [Crossref]
13. Büyüktuna SA, Hasbek M, Çelik C, et al. Klebsiella pneumoniae Infections in the Intensive Care Unit: Risk Factors Related to Carbapenem Resistance and Patient Mortality. Mikrobiyol Bul. 2020; 54(3): 378-91. [Crossref]
14. Durdu B, Hakyemez IN, Bolukcu S, Okay G, Gultepe B, Aslan T. Mortality markers in nosocomial Klebsiella pneumoniae bloodstream infection. Springerplus. 2016; 5(1): 1892. [Crossref]

15. Delle Rose D, Sordillo P, Gini S, et al. Microbiologic characteristics and predictors of mortality in bloodstream infections in intensive care unit patients: A 1-year, large, prospective surveillance study in 5 Italian hospitals. Am J Infect Control. 2015; 43(11): 1178-83. **[Crossref]**

16. Cekin ZK, Oncul A, Bayraktar B. Bloodstream Infections Caused by Multidrug Resistant Bacteria: Clinical and Microbiological Features and Mortality. Sisli Etfal Hastan Tıp Bul. 2023; 57(3): 416-25. **[Crossref]**

17. Scales DC, Thiruchelvam D, Kiss A, Redelmeier DA. The effect of tracheostomy timing during critical illness on long-term survival. Crit Care Med. 2008; 36(9): 2547-57. **[Crossref]**

18. Flaatten H, Gjerde S, Heimdal JH, Aardal S. The effect of tracheostomy on outcome in intensive care unit patients. Acta Anaesthesiol Scand. 2006; 50(1): 92-8. **[Crossref]**

19. Marsik C, Kazemi-Shirazi L, Schickbauer T, et al. C-reactive protein and all-cause mortality in a large hospital-based cohort. Clin Chem. 2008; 54(2): 343-9. **[Crossref]**

20. Chen PL, Li ZH, Yang HL, et al. Associations Between High-Sensitivity C-Reactive Protein and All-Cause Mortality Among Oldest-Old in Chinese Longevity Areas: A Community-Based Cohort Study. Front Public Health. 2022; 10: 824783. **[Crossref]**

21. Jin X, Li J, Sun L, et al. Prognostic Value of Serum Albumin Level in Critically Ill Patients: Observational Data From Large Intensive Care Unit Databases. Front Nutr. 2022; 9: 770674. **[Crossref]**

22. Yang K, Yang N, Sun W, et al. The association between albumin and mortality in patients with acute kidney injury: a retrospective observational study. BMC Nephrol. 2023; 24(1): 332. **[Crossref]**

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RESEARCH ARTICLE

Effects of clear aligner treatment on periodontal health: a bibliometric study

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ABSTRACT

Objective: The purpose of this study was to present a bibliometric analysis of scientific articles on clear aligner treatment (CAT) on periodontal health.

Materials and Methods: Papers published through July 5, 2023, were searched on the Web of Science (WOS). From a total of 63 papers, the top 25 most cited and appropriate for the study topic were selected.

Results: The most cited article with 82 citations was the article published in the European Journal of Orthodontics in 2015. The American Journal of Orthodontics and Dentofacial Orthopedics had the highest publication rate, with three of the top 25 articles published. The first author of the first article was Gabriele Rossini, among the top 25 highly cited articles evaluating the effect of CAT on periodontal health. Italy stands out as the country with the highest number of first authors with 9 articles, followed by China with 7 authors.

Conclusions: The bibliometric analysis provides significant information regarding the total number of publications and citations on clear aligner treatment on periodontal health. This bibliometric analysis provides a perspective on the progress of research on clear aligner treatment on periodontal health.

Keywords: Bibliometric analysis, clear aligner treatment, orthodontics, periodontal health

INTRODUCTION

Clear Aligners (CA) have been used as orthodontic appliances for many years, and the use of CA in adult patients has been increasing with the rise in aesthetic concerns. In addition to the aesthetic benefits of CA, it allows patients to perform functions such as speaking and eating more comfortably. It has advantages for orthodontists such as reducing chair time and reducing the development of events requiring emergency intervention. On the other hand, the need for good patient cooperation and cost can be shown as disadvantages for orthodontists (1-3).

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The American Academy of Periodontology (AAP) defines periodontal health as follows: The ability of the patient to function without abnormalities. The AAP uses parameters such as attachment level, probing depth, and bone loss to determine periodontal health and defines a healthy or diseased periodontium. A healthy periodontium improves an individual's quality of life, both physically and psychologically (4).

Bibliometrics is a set of literature reviews that show the historical development of scientific articles published on a given topic, such as country of publication and authors. Bibliometric analyses aim to provide an up-to-date approach to a given topic and measure the number of citations of articles on that topic. (4,5). CA appliances affect the oral health of individuals. It may increase the plaque index of patients undergoing treatment. There are studies suggesting that CA treatment does not have a negative effect on the periodontal health of patients (5,6). The purpose of this study is to present a bibliometric analysis of scientific publications on this subject.

MATERIALS AND METHODS

The purpose of this study is to conduct a bibliometric analysis of articles published on the periodontal health of patients undergoing clear aligner treatment. The characteristics of the publications—such as authors, study design, publication years, and citation counts—are analyzed to illustrate the impact of clear aligner treatment on periodontal health.

Only one researcher collected all data on July 5, 2023. Before the data collection process, the 5 most frequently used words were determined in related articles. In this bibliometric analysis, the most frequently used keywords were selected by looking at their synonyms to determine the articles to be scanned. The synonyms and compatibility of the words were used from the website https://www.ncbi.nlm.nih.gov/mesh. Keywords were determined from the most cited articles.

Articles published until July 5, 2023 were searched in Web of Science (WOS) by a single researcher (F.A.) using the formulation ALL=(clear aligner) AND ALL=(periodontal health). A total of 63 articles published in WOS were identified. The first 25 articles with the highest number of citations were selected. The 2 articles in the top 25 most cited articles were not included in the study because they were in vitro studies.

RESULTS

The top 25 articles published in Web of Science before July 5, 2023 were selected in descending order of citation. The most cited article with 82 citations was the article published in the European Journal of Orthodontics in 2015. The least cited article, with 5 citations among the top 25 on the subject, was the article published in Medicine in 2021. The top 25 most cited articles evaluating the effect of CAT on periodontal health are shown in Table 1.

The American Journal of Orthodontics and Dentofacial Orthopedics had the highest publication rate with three of the top 25 articles published. The journal with the highest JCR®IF2022 rate was Progress in Orthodontics with a rate of 4.8. The journals in which the top 25 most cited articles evaluating the effect of CAT on periodontal health were published and the impact factor for 2022 are presented in Table 2.

Among the top 25 highly cited articles evaluating the effect of CAT on periodontal health, the first author of the 1st article was Gabriele Rossini (7), while the first author of the 25th article was Yuan Wu (8). In the top 25 articles, only Stefano Mummolo has 2 articles. The top 10 first authors are presented in Table 3.

Table 4 shows the number of countries of first authors. Italy stands out as the country with the highest number of first authors with 9 articles, followed by China with 7 authors.

Table 1. The 25 most cited articles on periodontal health in the treatment of clear aligners

Rank	Paper	Citation Count (WOS)	Citation count in all databases	Type of manuscript
1	Rossini G, Parrini S, Castroflorio T, Deregibus A, Debernardi CL. Periodontal health during clear aligners treatment: a systematic review. Eur J Orthod. 2015 Oct;37(5):539-43.	82	87	Review
2	Jiang Q, Li J, Mei L, Du J, Levrini L, Abbate GM, Li H. Periodontal health during orthodontic treatment with clear aligners and fixed appliances: A meta-analysis. J Am Dent Assoc. 2018 Aug;149(8):712-720.e12	55	60	Review
3	Papageorgiou SN, Koletsi D, Iliadi A, Peltomaki T, Eliades T. Treatment outcome with orthodontic aligners and fixed appliances: a systematic review with meta-analyses. Eur J Orthod. 2020 Jun 23;42(3):331-343.	54	54	Review
4	Chhibber A, Agarwal S, Yadav S, Kuo CL, Upadhyay M. Which orthodontic appliance is best for oral hygiene? A randomized clinical trial. Am J Orthod Dentofacial Orthop. 2018 Feb;153(2):175-183.	39	42	Article
5	Contaldo M, Lucchese A, Lajolo C, Rupe C, Di Stasio D, Romano A, Petruzzi M, Serpico R. The Oral Microbiota Changes in Orthodontic Patients and Effects on Oral Health: An Overview. J Clin Med. 2021 Feb 16;10(4):780.	38	38	Review
6	Cassetta M, Altieri F, Pandolfi S, Giansanti M. The combined use of computer-guided, minimally invasive, flapless corticotomy and clear aligners as a novel approach to moderate crowding: A case report. Korean J Orthod. 2017 Mar;47(2):130-141.	24	25	Article
7	Mummolo S, Tieri M, Nota A, Caruso S, Darvizeh A, Albani F, Gatto R, Marzo G, Marchetti E, Quinzi V, Tecco S. Salivary concentrations of Streptococcus mutans and Lactobacilli during an orthodontic treatment. An observational study comparing fixed and removable orthodontic appliances. Clin Exp Dent Res. 2020 Apr;6(2):181-187.	23	27	Article
8	Mummolo S, Nota A, Albani F, Marchetti E, Gatto R, Marzo G, Quinzi V, Tecco S. Salivary levels of Streptococcus mutans and Lactobacilli and other salivary indices in patients wearing clear aligners versus fixed orthodontic appliances: An observational study. PLoS One. 2020 Apr 24;15(4): e0228798.	22	22	Article
9	Zhao R, Huang R, Long H, Li Y, Gao M, Lai W. The dynamics of the oral microbiome and oral health among patients receiving clear aligner orthodontic treatment. Oral Dis. 2020 Mar;26(2):473-483.	22	23	Article
10	Han JY. A comparative study of combined periodontal and orthodontic treatment with fixed appliances and clear aligners in patients with periodontitis. J Periodontal Implant Sci. 2015 Dec;45(6):193-204.	20	22	Article
11	Zhang B, Huang X, Huo S, Zhang C, Zhao S, Cen X, Zhao Z. Effect of clear aligners on oral health-related quality of life: A systematic review. Orthod Craniofac Res. 2020 Nov;23(4):363-370.	17	18	Review
12	Sifakakis I, Papaioannou W, Papadimitriou A, Kloukos D, Papageorgiou SN, Eliades T. Salivary levels of cariogenic bacterial species during orthodontic treatment with thermoplastic aligners or fixed appliances: a prospective cohort study. Prog Orthod. 2018 Aug 1;19(1):25.	17	19	Article

Table 1. Continued

Rank	Paper	Citation Count (WOS)	Citation count in all databases	Type of manuscript
13	Madariaga ACP, Bucci R, Rongo R, Simeon V, D'Antò V, Valletta R. Impact of Fixed Orthodontic Appliance and Clear Aligners on the Periodontal Health: A Prospective Clinical Study. Dent J (Basel). 2020 Jan 2;8(1):4.	15	15	Article
14	Guo R, Zheng Y, Liu H, Li X, Jia L, Li W. Profiling of subgingival plaque biofilm microbiota in female adult patients with clear aligners: a three-month prospective study. PeerJ. 2018 Jan 2;6: e4207. .	15	15	Article
15	Lin E, Julien K, Kesterke M, Buschang PH. Differences in finished case quality between Invisalign and traditional fixed appliances. Angle Orthod. 2022 Mar 1;92(2):173-179.	13	13	Article
16	Yassir YA, Nabbat SA, McIntyre GT, Bearn DR. Clinical effectiveness of clear aligner treatment compared to fixed appliance treatment: an overview of systematic reviews. Clin Oral Investig. 2022 Mar;26(3):2353-2370.	13	14	Review
17	Ma Y, Li S. The optimal orthodontic displacement of clear aligner for mild, moderate and severe periodontal conditions: an in vitro study in a periodontally compromised individual using the finite element model. BMC Oral Health. 2021 Mar 10;21(1):109.	13	15	Article
18	Sfondrini, Maria Francesca, et al. "Microbiological changes during orthodontic aligner therapy: A prospective clinical trial." Applied Sciences 11.15 (2021): 6758.	8	8	Article
19	Oikonomou E, Foros P, Tagkli A, Rahiotis C, Eliades T, Koletsi D. Impact of Aligners and Fixed Appliances on Oral Health during Orthodontic Treatment: A Systematic Review and Meta-Analysis. Oral Health Prev Dent. 2021 Jan 7;19(1):659-672.	8	8	Review
20	Levrini L, Mangano A, Margherini S, Tenconi C, Vigetti D, Muollo R, Marco Abbate G. ATP Bioluminometers Analysis on the Surfaces of Removable Orthodontic Aligners after the Use of Different Cleaning Methods. Int J Dent.2016:5926941.	8	9	Article
21	Miyamoto T, Lang M, Khan S, Kumagai K, Nunn ME. The clinical efficacy of deproteinized bovine bone mineral with 10% collagen in conjunction with localized piezosurgical decortication enhanced orthodontics: A prospective observational study. J Periodontol. 2019 Oct;90(10):1106-1115.	7	7	Article
22	Shokeen B, Viloria E, Duong E, Rizvi M, Murillo G, Mullen J, Shi B, Dinis M, Li H, Tran NC, Lux R, Wu T. The impact of fixed orthodontic appliances and clear aligners on the oral microbiome and the association with clinical parameters: A longitudinal comparative study. Am J Orthod Dentofacial Orthop. 2022 May;161(5): e475-e485	6	6	Article
23	Macrì, M., Murmura, G., Varvara, G., Traini, T., & Festa, F. Clinical performances and biological features of clear aligners materials in orthodontics. Frontiers in Materials, (2022): 819121	6	6	Review
24	Liu L, Song Q, Zhou J, Kuang Q, Yan X, Zhang X, Shan Y, Li X, Long H, Lai W. The effects of aligner overtreatment on torque control and intrusion of incisors for anterior retraction with clear aligners: A finite-element study. Am J Orthod Dentofacial Orthop. 2022 Jul;162(1):33-41.	5	5	Article
25	Wu Y, Cao L, Cong J. The periodontal status of removable appliances vs fixed appliances: A comparative meta-analysis. Medicine (Baltimore). 2020 Dec 11;99(50): e23165.	5	5	Review

Table 2. The journals and JCR®IF-2022 of the publications

	Paper Numbers	JCR® IF2022	Quartile Category
EUROPEAN JOURNAL OF ORTHODONTICS**	2	2.6	Q3
JOURNAL OF THE AMERICAN DENTAL ASSOCIATION**	1	3.9	Q1
AMERICAN JOURNAL OF ORTHODONTICS AND DENTOFACIAL ORTHOPEDICS**	3	3	Q2
JOURNAL OF CLINICAL MEDICINE**	1	3.9	Q2
KOREAN JOURNAL OF ORTHODONTICS**	1	1.9	Q2
CLINICAL AND EXPERIMENTAL DENTAL RESEARCH*	1	---	---
PLOS ONE**	1	3.2	Q2
ORAL DISEASES**	1	3.8	Q2
JOURNAL OF PERIODONTAL AND IMPLANT SCIENCE**	1	1.9	Q4
ORTHODONTICS & CRANIOFACIAL RESEARCH**	1	3.1	Q2
PROGRESS IN ORTHODONTICS**	1	4.8	Q1
DENTISTRY JOURNAL*	1	---	---
PEERJ**	1	2.7	Q2
ANGLE ORTHODONTIST**	1	3.4	Q2
CLINICAL ORAL INVESTIGATIONS**	1	3.4	Q2
BMC ORAL HEALTH**	1	2.9	Q2
APPLIED SCIENCES-BASEL**	1	2.7	Q2
ORAL HEALTH & PREVENTIVE DENTISTRY**	1	1.6	Q4
INTERNATIONAL JOURNAL OF DENTISTRY*	1	---	---
JOURNAL OF PERIODONTOLOGY**	1	4.3	Q1
FRONTIERS IN MATERIALS**	1	3.2	Q3
MEDICINE**	1	1.6	Q3

* The journals are ESCI categorization. ** The journals are SCI-Expanded Web of Science categorization.

Table 3. Contribution of top 10 authors country and university

First Author	Institution	Country	Number of citations
Gabriele Rossini	University of Turin	Italy	82
Qian Jiang	Southwest Forestry University	China	55
Spyridon N Papageorgiou	University of Zurich	Switzerland	54
Aditya Chhibber	137 Benedict Ave-Norwalk	US	39
Maria Contaldo	Universita della Campania Vanvitelli	Italy	38
Michele Cassetta	Sapienza University of Rome	Italy	24
Stefano Mummolo*	University of L'Aquila	Italy	23-22
Rui Zhao	Zhengzhou University	China	22
Ji-Young Han	Hanyang University	South Korea	20
Bo Zhang	Sichuan University	China	17

*There are two articles of the related author for the top 10 first-time authors whose article is most cited.

Table 4. Contribution of each country to research on clear aligner treatment on periodontal health

Country	Number
Italy	9
China	7
USA	4
Greece	2
Switzerland	1
South Korea	1
United Kingdom	1

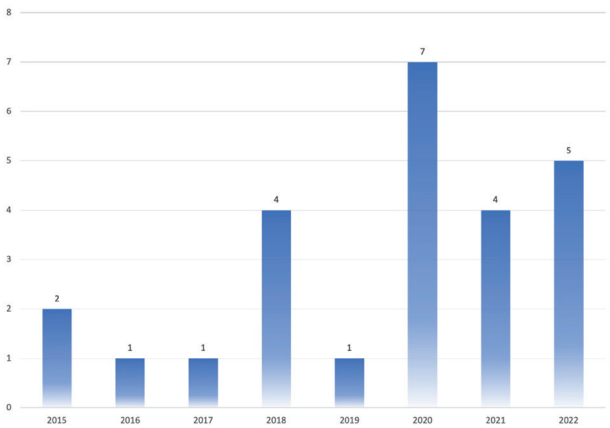

Figure 1. The annual number of publications.

Figure 2. Word cloud of countries where research has been conducted on the effects of clear aligners on periodontal tissues.

DISCUSSION

After the 2000s, the use of clear aligners became widespread due to intense commercialization. Particularly in recent years, the increased use of CA in orthodontic treatment has also played a major role in patients' preference for clear aligners due to improved aesthetics and comfort (9,10). This widespread clinical use has led researchers to focus on this popular topic, and in recent years, more than 600 articles on this subject have been published in the Web of Science Core Collection database (11). Bibliometric analysis is used to quantitatively and qualitatively examine this scientific research (12). Although this method of analysis is used in many areas of dentistry (13-15), there is no bibliometric study in the literature investigating the effect of CAT on periodontal health. The aim of this study was to evaluate the scientific studies carried out until July 5, 2023, in order to fill the gap in this field. This study was conducted by selecting the search terms "clear aligner" and "periodontal health" to find and evaluate relevant articles in the WOS database. It can be seen that in recent years there has been an increase in the years of the 25 most cited articles on the subject. The year with the highest number of publications was 2020 with 7 publications. At the same time, the most cited article was published in 2015 (Figure 1). Upon evaluating the countries of origin of the authors, it was found that Italy had the highest number of representation (Figure 2). The top three most cited articles originated from Italy, China, and Switzerland, respectively (Figure 3). While three journals were not classified within the Category Quartile of the Science Citation Index Expanded (SCIE), 44% of the articles were published in Q2 journals. Most of the published studies were research articles (64%) and review articles (36%). It is a natural process that the number of citations increases as the publication duration of an article extends. In this bibliometric study, the fact that the most cited article, published in 2015 with 82 citations, is from the earliest year among the 25 articles reviewed does not contradict the explanation regarding the relationship between citation rates and time. The fact that the most articles on the subject were 7 in 2020 and 4 in 2021 shows that there has been an increasing number of studies on the subject in recent years. It can be said that many

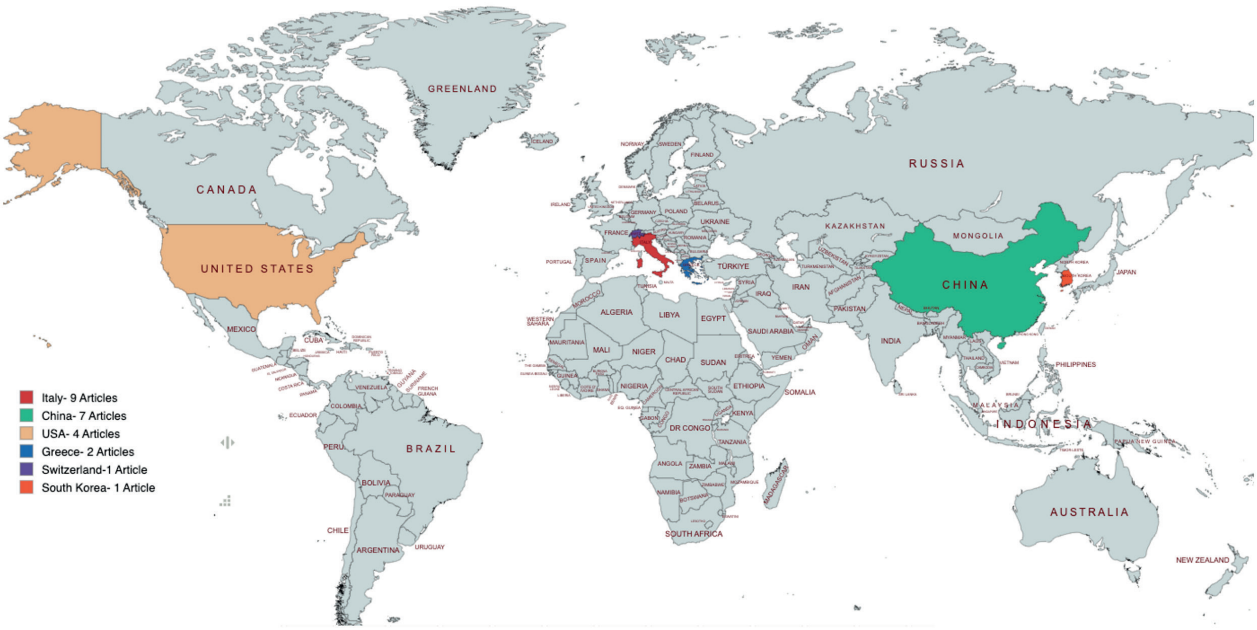

Figure 3. Global distribution of research on the effects of clear aligners on periodontal tissues.

issues such as the type of study and the method of the article influence the citation rates. Clear aligners have recently taken their place in clinical practice with rapidly developing technology. It is thought that since it has taken its place in clinical practice, it has caused academicians to focus on this field and conduct more studies. At the same time, the effects of various orthodontic treatment methods on periodontal health are always a subject worthy of research. For this reason, the effects of clear aligners on periodontal health have been a matter of curiosity. In the bibliometric analysis conducted by Bruni et al. on transparent aligners, one of the most searched keywords is "periodontal health" (12). Nevertheless, the fact that the most articles on this subject in this study are 7 in 2020 and 5 in 2022 indicates that although research on this topic has increased in recent years, well-designed studies on this subject are still lacking.

Limitations

The limitations of this study are that it provides data up to the date of data collection (July 5, 2023). Updated new studies should be conducted again for the research conducted after this date. Another limitation is that only the Web of Science database was used as the research platform, and using different keywords or databases may yield different results.

CONCLUSIONS

It is estimated that the use of clear aligners in clinical practice will increase day by day due to the growing aesthetic concerns of patients, the comfort of clear aligners, and the rapidly developing technology. With increasing clinical use, the effects of clear aligners on teeth and supporting tissues will also be discussed. Bibliometric analyses on various topics will draw researchers' attention to issues that have not been widely discussed in the literature. Thus, knowledge will be gained about many topics in literature. The aim is to ensure that the data provided is free of errors, especially by using developing artificial intelligence technologies both in clinical practice and in academic studies such as bibliometric analyses.

Ethical approval

Since this study is a bibliometric analysis, ethics committee permission is not required.

Author contribution

Concept: MT, SKB; Design: MT, SKB; Data Collection or Processing: HA, FA; Analysis or Interpretation: SKB; Literature Search: HA, FA; Writing: MT, SKB, HA. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Wheeler TT. Orthodontic clear aligner treatment. Semin Orthod. 2017; 23(1): 83-9. **[Crossref]**
2. Zheng M, Liu R, Ni Z, Yu Z. Efficiency, effectiveness and treatment stability of clear aligners: a systematic review and meta-analysis. Orthod Craniofac Res. 2017; 20(3): 127-33. **[Crossref]**
3. Gou Y, Ungvijanpunya N, Chen L, Zeng Y, Ye H, Cao L. Clear aligner vs fixed self-ligating appliances: orthodontic emergency during the 2020 coronavirus disease 2019 pandemic. Am J Orthod Dentofacial Orthop. 2022; 161(4): e400-6. **[Crossref]**
4. Mariotti A, Hefti AF. Defining periodontal health. BMC Oral Health. 2015; 15(Suppl 1): S6. **[Crossref]**
5. Needleman I, McGrath C, Floyd P, Biddle A. Impact of oral health on the life quality of periodontal patients. J Clin Periodontol. 2004; 31(6): 454-7. **[Crossref]**
6. Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM. How to conduct a bibliometric analysis: an overview and guidelines. J Bus Res. 2021; 133: 285-96. **[Crossref]**
7. Rossini G, Parrini S, Castroflorio T, Deregibus A, Debernardi CL. Periodontal health during clear aligners treatment: a systematic review. Eur J Orthod. 2015; 37(5): 539-43. **[Crossref]**
8. Wu Y, Cao L, Cong J. The periodontal status of removable appliances vs fixed appliances: a comparative meta-analysis. Medicine (Baltimore). 2020; 99(50): e23165. **[Crossref]**
9. Rosvall MD, Fields HW, Ziuchkovski J, Rosenstiel SF, Johnston WM. Attractiveness, acceptability, and value of orthodontic appliances. Am J Orthod Dentofacial Orthop. 2009; 135(3): 276-7. **[Crossref]**
10. Fujiyama K, Honjo T, Suzuki M, Matsuoka S, Deguchi T. Analysis of pain level in cases treated with Invisalign aligner: comparison with fixed edgewise appliance therapy. Prog Orthod. 2014; 15(1): 64. **[Crossref]**
11. Gong B, Liu Z, Yang L, et al. Twenty years of clear aligner therapy: a bibliometric analysis (2002-2022). Australasian Orthodontic Journal. 2023; 39(2): 15-31. **[Crossref]**
12. Bruni A, Serra FG, Gallo V, Deregibus A, Castroflorio T. The 50 most-cited articles on clear aligner treatment: a bibliometric and visualized analysis. Am J Orthod Dentofacial Orthop. 2021; 159(4): e343-62. **[Crossref]**
13. Patil SS, Sarode SC, Sarode GS, et al. A bibliometric analysis of the 100 most cited articles on early childhood caries. Int J Paediatr Dent. 2020; 30(5): 527-35. **[Crossref]**
14. Alarcón MA, Esparza D, Montoya C, Monje A, Faggion CM. The 300 most-cited articles in implant dentistry. Int J Oral Maxillofac Implants. 2017; 32(1): e1-8. **[Crossref]**
15. Faggion CM, Málaga L, Monje A, Trescher AL, Listl S, Alarcón MA. The 300 most cited articles published in periodontology. Clin Oral Investig. 2017; 21(6): 2021-8. **[Crossref]**

NORTHWESTERN MEDICAL JOURNAL

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CASE REPORT

PAST, a novel solution for crossing another wire in the severely dissected peripheral artery

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ABSTRACT

The most prevalent symptom of lower limb artery occlusions is intermittent claudication. The most commonly used technique to treat symptomatic patients is balloon dilatation of the occlusive plaque. Balloon dilatation of the lesion may cause dissection. The dissected artery wiring is a challenging scene. First, we can implant a stent in the dissection and then use it to cross the sealed artery. Additionally, we can use dual lumen catheters or dual lumen balloon catheters. But sometimes, angiography labs do not have these modern devices. In the present case, we came up with a solution and successfully finished the procedure by using a balloon catheter to transfer the second guidewire, which cannot pass through the dissected lesion. We named the technique Peripheral Artery Sidecar Technique (PAST).

Keywords: Angioplasty, dissection, guidewire, peripheral artery

INTRODUCTION

Occlusive disorders of the lower extremity peripheral arteries most frequently occur in the superior femoral arteries (SFA) (1). The most often employed technique for treating patients is balloon dilatation of the occlusive plaque (2). However, balloon dilatation causes lumen enlargement due to the dissection and compression of the plaque (2,3). It takes quite a bit of work to insert a new guidewire into the dissected vascular segment because the wire frequently passes through the subintima. In this situation, the best course of action may be to secure the dissection flap to the vascular wall using long-term balloon dilatation or stent implantation before advancing the guidewire, but with the risk of stent thrombosis (4). Dual-lumen catheters may be another option for advancing a guidewire from the dissected artery (5). We would like to share a case where we came up with an alternative solution and successfully finished the procedure by using a balloon catheter to transfer the second guidewire, which cannot pass through the dissected lesion, Peripheral Artery Sidecar Technique (PAST).

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CASE PRESENTATION

We admitted a 54-year-old male patient who complained of intermittent claudication in the calf region. The lower extremity arterial Doppler ultrasound revealed monophasic flow in the right peroneal artery (PA), arteria tibialis anterior (ATA), and arteria tibialis posterior (ATP), along with total occlusion of the SFA. We planned a lower extremity peripheral angiography (PAG). It was observed that there was chronic total occlusion of the right SFA distal, and the PTA and peroneal artery were filled with well-developed collateral circulation originating from the deep femoral artery and SFA (Figure 1a, Video 1 and Video 2). Additionally, the ATA was weakly filled with the peroneal artery and collateral vessels originating from the PTA midregion (Figure 1b, Video 2). We parked a 7F 90 cm sheath (Flexor Shuttle-SL introducer guiding sheath, Cook, United States) in the right SFA, along with a 6F right Judkins diagnostic catheter. The 0.035'' NAVICROSS® Support Catheter (Terumo, Tokyo, Japan), along with a 0.035'' hydrophilic wire (Glidewire Advantage, Terumo, Tokyo, Japan), attempted to enter the PTA. However, the wire advanced subintimally and was unable to traverse into the distal true lumen. We also encountered failures with the Hi-Torque Winn 40 (Abbott, United States), Halberd (Asahi Intecc, Nagoya, Japan), and AstatoXS40 (Asahi Intecc, Nagoya, Japan) wires (Figure 2). The decision was made to perform a retrograde SFA occlusion by puncturing the PTA. The PTA was punctured with a 0.018'' Gladius (Asahi Intecc, Nagoya, Japan), and the distal cap was engaged with a 3.0x120 mm peripheral balloon (Sterling, Boston Scientific, USA) support (Figure 3a, Video 3). As the Gladius failed to progress, we advanced the Halberd wire (Asahi Intecc, Nagoya, Japan) with balloon support, ultimately passing the SFA true lumen (Figure 3b). The same 3.0x120 mm balloon dilated the lesion with pressures between 8 and 14 atm (Figure 3c). Instead of using the Halberd wire, we sent a 300 cm 0.014'' mm floppy wire (Choice Floppy Guidewire, Boston Scientific, USA) through the balloon that entered the SFA. We aimed to enter the 7F sheath in the SFA, externalize the wire from the left CFA, and execute the procedure in an antegrade manner (Figure 3D, Video 4). A 4.0x120 mm peripheral balloon (Sterling, Boston Scientific, USA) at 6-8 atm and a 5.0x150 mm peripheral balloon (Mustang, Boston Scientific, USA) at 6-8 atm were applied to the lesion over 0.014'' wires via the antegrade route (Figure 4a). Following balloon dilatation, the distal SFA had an optimal opening but a short dissecting aneurysmatic lesion that did not disrupt the flow (Figure 4b, Video 5). Once again, we observed that the ostium of the ATA, previously only weakly filled with collaterals from the distal, was now fully filled (Figure 4c). We planned to pass another

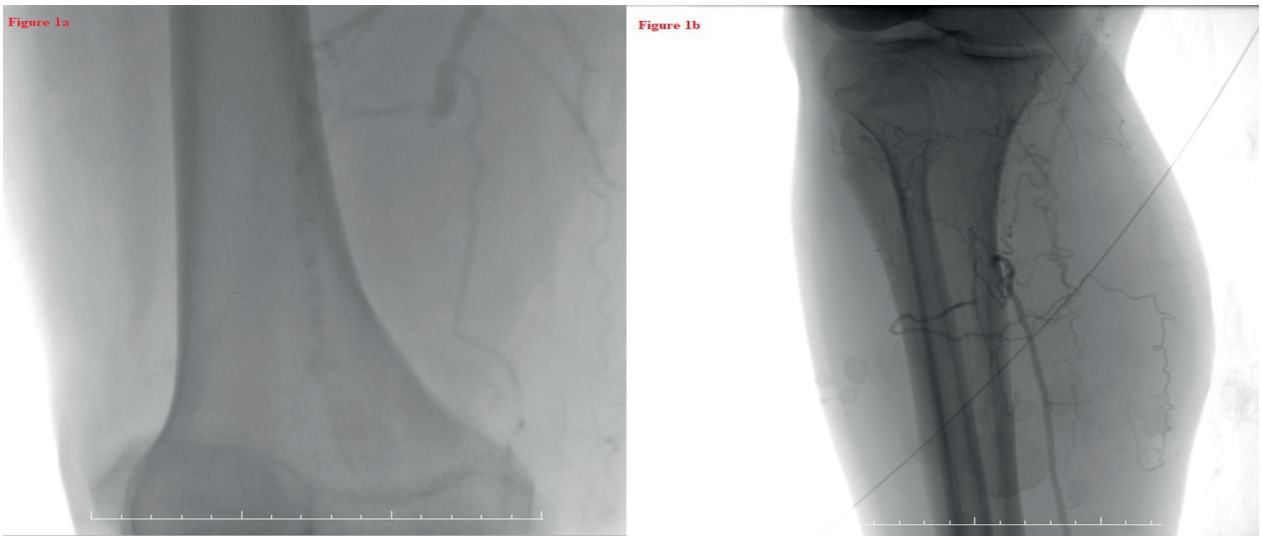

Figure 1. a: Chronic total occlusion of the right superficial femoral artery. **b:** Collateral filling of the right posterior tibial artery and peroneal artery, also weak filling of the right anterior tibial artery.

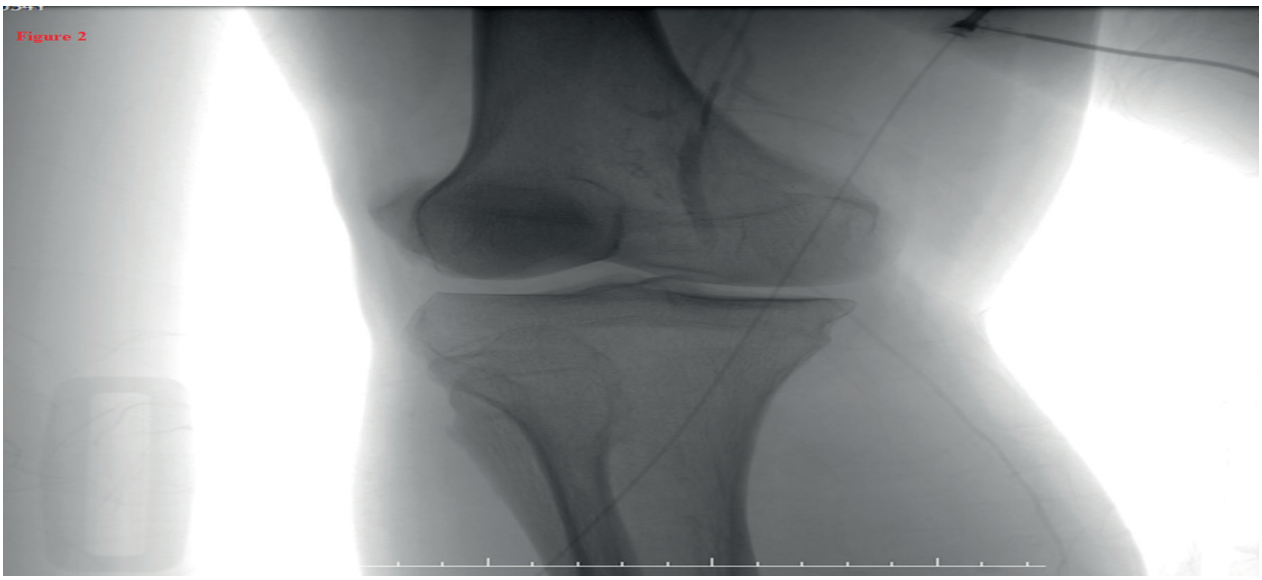

Figure 2. Dissected superior femoral artery with contrast staining of the false lumen.

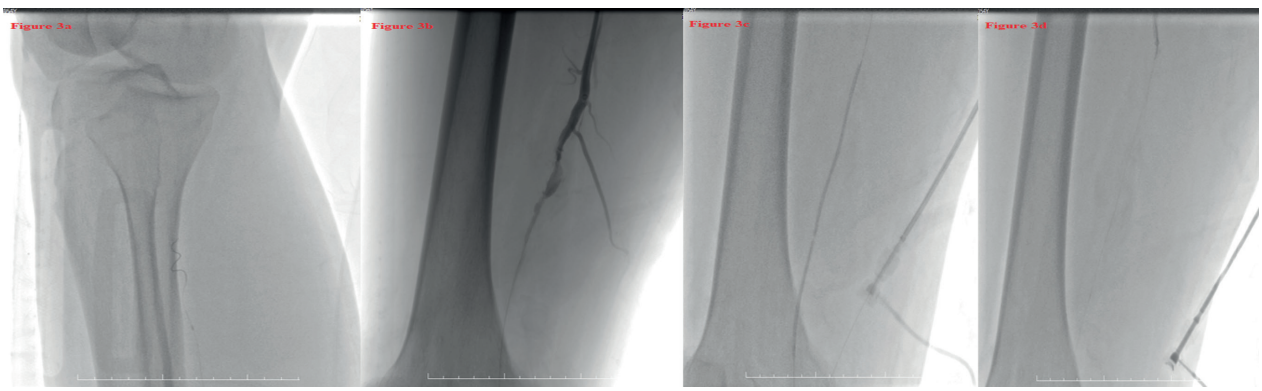

Figure 3. a: After the puncture of the distal posterior tibial artery, 0.018'' Gladius wire advanced and the distal cap was engaged with 3.0x120 mm peripheral balloon. **b:** Halberd wire was passed into the SFA true lumen. **c:** 3.0x120 mm balloon dilatated the lesion. **d:** A 300 cm 0.014'' mm floppy wire was sent instead of the Halberd wire through the balloon entering the SFA.

wire through the total occlusion in the ATA. However, we were unable to pass a second wire through the dissected lesion in the SFA. Since the angiography lab did not have a peripheral vascular dual-lumen catheter, we inflated the 4.0x120 mm balloon with air. This balloon had been used before to widen the SFA and PA. Next, we inflated the balloon to 4 atm using saline. A 23-gauge needle punctured the balloon at its proximal end. We gently inserted the needle into the balloon, but did not puncture the distal end. We inserted a Fielder FC guidewire (Asahi Intecc, Nagoya, Japan) and pushed it forward until the tip of the balloon. We held both the balloon and the inserted wire, then gently removed them from the needle. On the main guidewire, we held onto both the balloon and the wire and pushed both forward as a unit. We advanced the balloon as far distal as possible through the lesion, retracted the Fielder FC (Asahi Intecc, Nagoya, Japan) from the balloon,

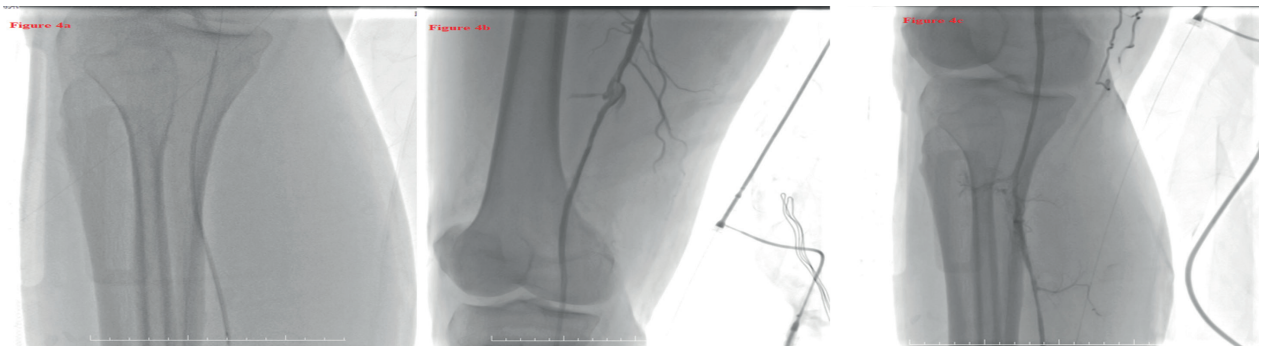

Figure 4. a: 4.0x120 mm and 5.0x150 mm peripheral balloons dilatation applied to the lesion over 0.014'' wires via antegrade route. **b:** After balloon dilatation, the lesion in the distal SFA had an optimal opening, but a short dissecting aneurysmatic lesion that did not disrupt the flow. **c:** The ostium of the ATA, which was only weakly filled with collaterals from the distal before, was filled.

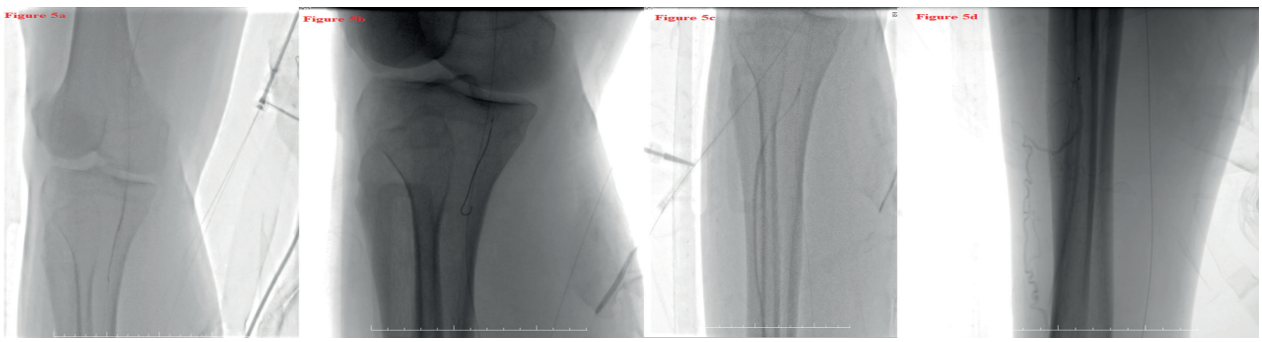

Figure 5. a: The sidecar balloon catheter transported the second wire through the dissected segment. **b:** The second wire was at the level of the ATA ostium. **c:** The ATA was dilated with a 3.0x150 mm peripheral balloon catheter. **d:** The final view of the ATA.

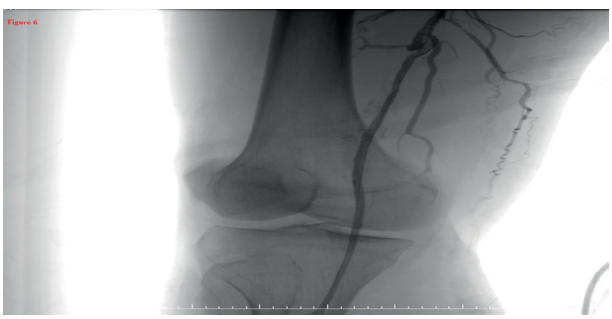

Figure 6. The dissected lesion in SFA was short and the flow was not disturbed.

and then advanced it again outside, parallel to the balloon (Figures 5a and 5b, Video 6). We removed the balloon catheter from the coronary artery. The Fielder FC wire passed the total occlusion lesion in the ATA and reached the ADP. The ATA was dilated at 12-16 atm with a 3.0x150 mm peripheral balloon catheter (Sterling, Boston Scientific, USA) (Figure 5c). We observed that the ATA lesion opened optimally, and the ADP began to fill antegradely (Figure 5d). We planned a medical follow-up because the dissected lesion in the SFA was short and the flow was not disrupted, leading us to terminate the procedure (Figure 6).

DISCUSSION

Occlusive disorders of the lower extremity peripheral arteries occur most frequently in the superior femoral arteries (SFA) (1). The most often employed technique for treating patients is balloon dilatation of the occlusive plaque (2). However, the dissection and compression of the plaque are the causes of the lumen enlargement brought on by balloon dilatation (2,3). It takes quite a bit of work to insert a new guidewire into the dissected vascular segment because the wire frequently passes through the subintima. It might be best to use long-term balloon dilatation or stent implantation to attach the dissection flap to the vascular wall before moving the guidewire forward, but there is a chance of stent thrombosis (4). Dual-lumen catheters may be another option for advancing a guidewire from the dissected artery (5). In our case, after SFA/PA balloon dilatation, we observed ATA antegrade filling, which was not visible before. However, since the SFA/PA occlusion crosses retrogradely from the PTA, withdrawing this wire and directing it to the ATA may not be appropriate. The complication occurs when the lesion forms a dissecting aneurysmatic lesion, which then passes through another guidewire and crosses the ATA occlusion, potentially losing the distal flow due to the lengthening of the dissection flap to the trifurcation point. As a result, we devised a method for passing a second guidewire through the dissected lumen from the side of the balloon catheter. We then send this guidewire over the externalized wire, which retrogrades the occluded segment. We named that technique PAST. During our literature research, we discovered a case report (6) applied this technique to coronary arteries. However, the literature does not demonstrate such an application in peripheral arteries. We present the first case in the literature that applies this technique to peripheral arteries. The PAST can be free, especially when a used balloon is recycled. The absence of the over-the-wire (OTW) portion of traditional dual-lumen catheters, which makes removal easier when the second guidewire is inserted, is a benefit. The PAST allows the use of any balloon size.

The PAST may not be as effective in the long, severely calcified, and tight CTO lesions (6). In comparison to a dedicated dual-lumen catheter, the steerability and directability of the second guidewire may be constrained. When the balloon catheter is inside the coronary artery, it is best to avoid attaching the cotransporter's hub to the indeflator to prevent air embolization. The crossing profile remains unchanged when advancing and retrieving the balloon, thereby reducing the risk of balloon retrieval failure in calcified lesions. The distal transfer may result in the loss of the wire. In this scenario, we can either remove the cotransporter, as the second wire has sufficiently migrated distally, or we must remove the wire first, followed by the cotransporter, thereby requiring a new round of the procedure.

The PAST presents a simple and inexpensive solution whenever a dual-lumen microcatheter or dual-lumen balloon is unavailable or inapplicable.

Ethical approval

Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: EA, ID; Concept: EA; Design: EA, YG; Data Collection or Processing: EA, TD, EO; Analysis or Interpretation: EA, YG, IAI; Literature Search: EA; Writing: EA, SI. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Armstrong EJ, Brodmann M, Deaton DH, et al. Dissections after infrainguinal percutaneous transluminal angioplasty: a systematic review and current state of clinical evidence. J Endovasc Ther. 2019; 26(4): 479-89. **[Crossref]**
2. Fujihara M, Takahara M, Sasaki S, et al. Angiographic dissection patterns and patency outcomes after balloon angioplasty for superficial femoral artery disease. J Endovasc Ther. 2017; 24(3): 367-75. **[Crossref]**
3. Voûte MT, Stathis A, Schneider PA, et al. Delphi consensus study toward a comprehensive classification system for angioplasty-induced femoropopliteal dissection: the DISFORM study. JACC Cardiovasc Interv. 2021; 14(21): 2391-401. **[Crossref]**
4. Banerjee S, Sarode K, Mohammad A, et al. Femoropopliteal artery stent thrombosis: report from the excellence in peripheral artery disease registry. Circ Cardiovasc Interv. 2016; 9(2): e002730. **[Crossref]**
5. Pyxaras SA, Galassi AR, Werner GS, et al. Dual lumen microcatheters for recanalisation of chronic total occlusions: a EuroCTO Club expert panel report. EuroIntervention. 2021; 17(12): e966-70. **[Crossref]**
6. Leibundgut G, Büttner HJ. A simple solution to deliver a second guidewire without a dual-lumen microcatheter-The sidecar technique. Clin Case Rep. 2021; 9(9): e04787. **[Crossref]**

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