Annals of Medical Research

The Official Journal of Inonu University Faculty of Medicine

Ann Med Res | **Volume: 32 | Issue: 5 | May 2025**

Original Articles

Case Reports

Annals of Medical Research

The Official Journal of Inonu University Faculty of Medicine

Editorial Board | Volume: 32 | Issue: 5 | May 2025

Annals of Medical Research

The Official Journal of Inonu University Faculty of Medicine

Editorial Advisory Board | Volume: 32 | Issue: 5 | May 2025

Annals of Medical Research

The Official Journal of Inonu University Faculty of Medicine

Table of Contents | **Volume: 32 | Issue: 5 | May 2025**

Original Articles

Case Reports

Ann Med Res

Current issue list available at Ann Med Res

Annals of Medical Research

journal page: annalsmedres.org

Clinical implications of morphometric evaluation of the posterior tibial curvature on the sagittal plane

Merve Kucuker [a,*], Nazli Ates [b], Mehmet Ali Malas [a]

[a] Izmir Katip Celebi University, Faculty of Medicine, Department of Anatomy, Izmir, Türkiye
[b] Bulent Ecevit University, Faculty of Medicine, Department of Anatomy, Zonguldak, Türkiye
*Corresponding author: mervedkucuker@gmail.com (Merve Kucuker)

MAIN POINTS

- The posterior tibial curvature is significantly greater in the proximal region than in the distal region.
- Understanding tibial curvature is essential for accurate surgical planning and avoiding postoperative complications.
- This study presents a practical morphometric method for evaluating posterior tibial curvature on the sagittal plane.

Cite this article as: Kucuker M, Ates N, Malas MA. Clinical implications of morphometric evaluation of the posterior tibial curvature on the sagittal plane . *Ann Med Res*. 2025;32(5):175--179. doi: 10.5455/annalsmedres.2024.12.261.

ABSTRACT

Aim: This study aimed to morphometrically examine the posterior tibial curvature (PTC) on the sagittal plane in the proximal and distal tibia regions.

Materials and Methods: Forty-eight (21 right, 27 left) dry tibia bones were used. Both linear and angular parameters were measured on ImageJ. Linear measurements: Tibiae were placed on a horizontal surface on their posterior face. Tibiae were photographed from the medial aspect. In the photographs, the distance between the proximal and distal contact points (proximal: C0P, distal: C0D) of the tibia with the horizontal plane was divided into eight equal parts by 7 (C1-C7) landmarks. From each landmark to the tibia, perpendiculars were drawn. The intersections of the perpendiculars with the posterior margin of the tibia were determined (C1'-C7'). The distances between corresponding landmarks were measured (H1-H7). The heights of the tibiae (L) were also measured. Angular measurements: Lines were drawn between each landmark on the proximal tibia and the proximal contact point of the tibia (C0P) for A1 to A3. Similarly, lines were drawn between each landmark on the distal tibia and the distal contact point of the tibia (C0D) for A5 to A7. Angles between these lines and horizontal lines measured (A1-A7).

Results: There were no statistically significant differences between right and left for all parameters. H1, H2 and H3 were statistically greater than the H7, H6 and H5, respectively. A1, A2 and A3 were statistically greater than the A7, A6 and A5, respectively. Sagittal distances and angles in the proximal region were observed to be higher than the distal region.

Conclusion: Tibial morphometry is crucial for treating tibial fractures, planning regional surgeries, assessing surgical outcomes, and preventing complications. We hope that the method proposed in this study will be preferred for evaluating the morphometric characteristics of the posterior curvature of the tibia, particularly in the context of tibial biomechanics or personalized surgical planning.

Keywords: Tibia, Posterior curvature, Morphometry, Anatomy

Received: Dec 08, 2024 **Accepted:** Mar 24, 2025 **Available Online:** May 26, 2025

INTRODUCTION

The tibia is essential for the lower extremity in carrying body weight of the humans. It helps to distribute body weight properly and keeps the body balanced. Previous studies have included morphological features and curvatures of lower extremity bones [1-7]. Features such as cross-sectional geometry, cortical thickness, trabecular bone architecture, and longitudinal curvature of the diaphysis of long bones are among the morphological features that ultimately affect the mechanical performance of the lower extremities [8]. Curvatures of long bones cause increased tension levels in the bone [1-4]. Studies have shown that curvatures of long bones are associated with activity level and movement, and even these curvatures cannot develop sufficiently without mechanical load [1].

While there are many studies about femoral curvature, studies on the causes and biomechanics of femoral curvature [6, 9] and characteristics of posterior tibial curvature (PTC) are quite limited. According to a study examining tibial curvature among Central European agriculturalists by the historical era, there was a simultaneous decrease in tibial curvature and rigidity seen in the medieval and iron ages compared to prehistoric times. This difference was evident in the middle diaphysis re-

gion [5]. In addition, although this study suggests that tibial curvature may be more strongly associated with mobility than body size, it also emphasizes that several complex factors play a role in defining the tibial curvature of the diaphysis and require further study [5].

In rats deprived of mechanical function by unilateral sciatic neurectomy during the growth period, the curvature decreased on the side where the neurectomy was performed, but the length of the tibia was not affected [10]. The distinction between the physiological or pathological curvatures of the tibia is also discussed in the literature. Clinicians need to know the normal range of PTC, especially since curvatures seen in pathological conditions such as genu varum/valgum, rickets, and osteogenesis imperfecta in children require treatment such as osteotomy [11]. A radiographic study found that the depth of sagittal tibia curvature decreases with age in children, establishing age-related average values for physiological tibial curvature [12].

Considering that the bone curvatures are affected by tension on the bone, it is necessary to analyze the morphological characteristics of the tibia well in plaque, screw or prosthesis applications to be placed in the region in surgical interventions to be applied to the patient in cases such as bone fractures or osteoarthritis. Studies emphasize the importance of understanding the details of tibia morphology in surgical interventions such as prostheses and screw applications to be applied on the proximal region of the tibia, especially in knee joint surgery [13]. A comprehensive understanding of tibia morphology may be important for optimizing treatment outcomes and facilitating the healing process in tibial fractures, pathologies, and associated surgical or prosthetic interventions.The aim of this study was to morphometrically investigate the PTC and its associated angles, in the proximal and distal regions of the tibia on the sagittal plane.

MATERIALS AND METHODS

This study was performed on 48 (21 right, 27 left) dry tibia bones in the Anatomy Laboratory of the Izmir Katip Celebi University Faculty of Medicine. The bones with structural deformities that could impact the study's results were excluded. There were no age or gender records of the bones. A match could not be made, indicating whether the right and left tibia bones belong to the same individual. The study was approved by our institutional review board for scientific ethical conduct (Izmir Katip Celebi University Non-Interventional Clinical Research Ethics Committee, Decision No: 0312). Morphometric measurements were evaluated on dry tibia bones and digital image of these bones.

Photograph acquisition

Two digital cameras, Canon EOS 800D and Nikon Coolpix S570, were used to photograph the PTC. A water level gauge ensured that the angle between the digital cameras and the bone surfaces relative to the coronal plane was maintained at 0°. The dry tibia bone was placed horizontally on a table equipped with a water gauge, with the posterior margin facing the table edge, and stabilized using play dough (Figure 1). The first camera was placed superior to the bone to observe the superior articular surface of the tibia. The second camera was placed at level of the table and medial to the bone at a fixed distance and angle. A ruler was placed on the table to calibrate the measurements. To standardize the position of the tibia, the transcondylar axis (parallel to the table) passing through the midpoint of the tibial condyles was aligned with the horizontal grid line using the grid view mode of the first camera. The tibia was then fixed with play dough. The second camera was used to capture medial views of the bone (Figure 1). Measurements were performed on the medical images obtained.

Figure 1. Image of the left dry tibial bone taken from the medial side.

Determination of sagittal neasurements

The measurement points were first identified by examining medial view photographs of dry tibia bones. The tibiae were placed on a horizontal surface on their posterior face to establish these points. The proximal point where the tibia made contact with the horizontal surface was labelled "C0P", and the distal contact point was labelled "C0D" (Figure 2).

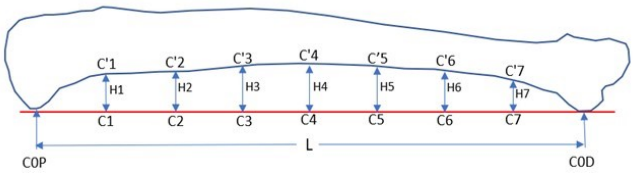

Figure 2. Schematic representation of the sagittal distances between the posterior tibial curvature of left dry tbia bone and the horizontal plane. (C0P: Proximal contact point, C0D: Distal contact point. C1-C7: Landmarks on the horizontal plane, C'1-C'7: Landmarks on the posterior margin of the tibia, H1-H7: Sagittal distances, L: Height of the tibia).

The distance between the proximal and distal contact points (proximal: C0P, distal: C0D) was considered the height (L) tibia with the horizontal plane divided into eight equal parts by 7 (C1-C7) landmarks (Figure 2). From each landmark to the tibia, perpendiculars were drawn. The intersections of the perpendiculars with the posterior margin of the tibia were determined (C1'-C7'). The distances between corresponding landmarks were measured (H1-H7) (Figure 2). The sagittal distances between corresponding landmarks (H1-H7) were measured separately (C1=C1', H1; C2=C2', H2; C3=C3', H3; C4=C4', H4; C5=C5', H5; C6=C6', H6; C7=C7', H7)

https://doi.org/10.5455/annalsmedres.2024.12.261

(Figure 2). H1, H2, and H3, representing the sagittal distances were considered proximal region distances. The H4 was classified as the median distance, while H5, H6, and H7 were considered distal region distances.

Determination of angular parameters

Lines were drawn from each proximal landmark (C1'-C3') to the proximal contact point (C0P) to form the proximal region angles A1-A3 (Figure 3). Similarly, lines were drawn from each distal landmark (C5'-C7') to the distal contact point (C0D) to form the distal region angles A5-A7 (Figure 3). The angle between C4' and the C0P/C0D points was symmetrical, and these angles were considered equal (Figure 3). The angles between these lines and the horizontal plane were measured (A1-A7).

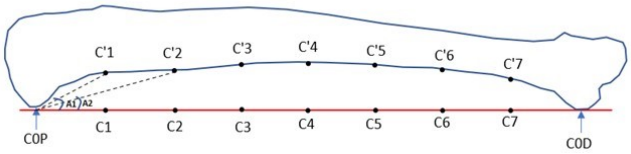

Figure 3. Schematic representation of the A1-A7 angles between the posterior tibial curvature of left dry tbia bone and the horizontal plane. (C0P: Proximal contact point, C0D: Distal contact point. C1-C7: Landmarks on the horizontal plane, C'1-C'7: Landmarks on the posterior margin of the tibia, A1: The angle between three points (C'1-C0P-C0D), A2: The angle between three points (C'2-C0P-C0D)).

The Image J program (Rasband, W.S., ImageJ, U.S. National Institutes of Health, Bethesda, Maryland, USA, https://imagej.nih.gov/ij/, 1997-2018) was used to perform the angular and sagittal measurements. Two researchers independently repeated these measurements, ensuring no intra- or inter-observer variability. In addition, intra-observer and inter-observer correlation coefficients were calculated to assess observer consistency. The measurements were performed separately by the researchers. There were no significant differences in intra-observer and inter-observer measurements.

Statistical analysis

The data were analyzed using statistical software package for social sciences version 25 (SPSS 25.0) (IBM Corp., Armonk, New York, USA). Descriptive statistics for the variables were presented as the number of observations, minimum and maximum values, and median (IQR). The normality of the data was assessed using the Shapiro-Wilk test. An independent samples T-test was used to compare side and proximal-distal measurements for data with a normal distribution, while the Mann-Whitney U test was applied for non-normally distributed data. Any p value < 0.05 was considered as statistical significance. The analyses were performed using 95% confidence interval.

RESULTS

In this study, a total of 48 dry tibia bones were used, consisting of 21 right and 27 left tibias. No significant difference was found between right and left side in terms of tibial height (L) as defined in our study ($p > 0.05$). The median tibial height was 301,25 mm (Table 1). The median (interquartile range, IQR), and range (minimum-maximum) of the sagittal distances (H1-H7) and angular parameters (A1-A7), categorized by side (right/left) and tibial region (proximal/median/distal), are presented in Table 1 and Table 2, respectively. All parameters had no statistically significant differences between right and left side ($p > 0.05$).

There was a significant difference in the comparison of the H1-H7, H2-H6, and H3-H5 parameters between the proximal and distal sagittal distances on both the right and left sides ($p<0.001$, Table 2). H4 is a median distance, and median (IQR) result is 19,35 (4,41) mm (Table 1). There was a significant difference in the comparison of the A1-A7, A2-A6, and A3-A5 parameters between the proximal and distal sagittal distances on both the right and left sides ($p<0.001$, Table 2). Sagittal distances and angles in the proximal region were observed to be higher than the distal region.

DISCUSSION

The tibia is one of the bones that is essential for carrying the human body weight. It maintains the balance of the body by distributing its weight evenly in the lower extremity. However, studies have shown that the curvatures of long bones develop with activity level, movement and mechanical loading [1]. Studies on posterior tibial curvature seen in the tibia are quite limited. In our study, it was aimed to examine the PTC and related angles morphometrically in the proximal and distal regions of the tibia in the sagittal plane in the limited number of tibial bones in our laboratory. We performed a preliminary evaluation of the data regarding posterior tibial curvature obtained in our study.

The results showed no significant difference between the right and left sides in tibial height (L) or the sagittal distances (H1-H7), but the sagittal distances on the right side were greater than on the left side (Table 1). A similar pattern was observed in the angular measurements (A1-A7), where the angles on the right side were greater than those on the left (Table 2). These quantitative differences may be attributed to the small sample size or the fact that the dry bones from each side did not belong to the same individual. Additionally, the greater sagittal distances and angles observed on the right side may indicate that the dominant limb is subjected to different biomechanical forces, influencing bone curvature.

Macintosh et al. [5] comparatively examined the curvature of farmers' dry tibia bones at different ages in Central Europe. Using a 3D modelling method, they reported that tibial curvature in the middle diaphyseal region decreased from the Neolithic age to the middle age. They also found that this change was not affected by body size and tibia height. Their study

https://doi.org/10.5455/annalsmedres.2024.12.261

Table 1. Median (Interquartile Range (IQR)) and minimum–maximum (min–max) values for sagittal distances (H) in the proximal, median, and distal tibia regions of the right and left tibia (mm).

		Tibial Height (L)	Tibia Regions						
			Proximal**			Median***		Distal**	
			H1	H2	H3	H4	H5	H6	H7
Right* (R) N=21	Median (IQR)	294.10 (37.58)	16.82 (2.43)	18.58 (4.63)	20.74 (4.52)	20.44 (3.56)	18.60 (2.81)	16.51 (2.79)	12.83 (3.28)
	Min-max	271.57-349.27	8.32-22.97	7.99-25.14	9.32-26.62	9.66-25.88	8.99-25.52	7.66-22.92	5.33-18.49
Left* (L) N=27	Median (IQR)	307.53 (42.59)	15.29 (5.81)	17.11 (3.69)	18.24 (4.53)	18.57 (4.26)	16.74 (3.89)	14.03 (4.00)	10.69 (3.46)
	Min-max	186.42-352.24	10.23-22.99	10.42-23.99	10.42-24.59	11.18-26.28	9.62-24.89	8.02-21.14	8.02-21.14
Total N=48	Median (IQR)	301.25 (36.52)	16.44 (4.27)	17.63 (4.55)	19.03 (5.12)	19.35 (4.41)	17.94 (3.95)	15.07 (3.53)	11.48 (3.50)
	Min-max	186.42-352.24	8.32-22.99	7.99-25.14	9.32-26.62	9.32-26.62	8.99-25.52	7.66-22.92	5.06-23.55

**p>0.05: Comparison of sagittal distances (H1-H7) between right and left tibiae. **p<0.001: There was a significant difference in the comparison of the H1-H7, H2-H6, and H3-H5 parameters between the proximal and distal sagittal distances on both the right and left sides. *** p>0.05: There was no difference in the H4 sagittal distance measured from the median region on both the right and left sides.*

Table 2. Median (Interquartile Range (IQR)) and minimum–maximum (min–max) values for sagittal distances (H) in the proximal, median, and distal tibia regions of the right and left tibia (mm). for angles in the proximal, median, and distal tibia regions of the right and left tibia (mm).

		Tibia Regions						
		Proximal**			Median		Distal**	
		A1	A2	A3	A4	A5	A6	A7
Right* (R) N=21	Median (IQR)	23.07 (4.91)	12.74 (3.61)	10.60 (2.88)	7.75 (2.14)	9.50 (2.03)	12.13 (3.20)	18.98 (5.01)
	Min-max	14.04-31.78	6.37-20.11	5.15-14.24	4.11-10.86	5.13-13.89	6.57-18.81	10.59-29.27
Left* (L) N=27	Median (IQR)	23.96 (5.32)	12.74 (3.61)	9.37 (2.21)	7.01 (2.00)	8.63 (2.76)	10.45 (3.72)	16.16 (5.29)
	Min-max	8.66-31.14	5.94-17.71	4.82-11.94	4.79-9.59	6.31-12.04	8.09-15.43	11.1021.65
Total N=48	Median (IQR)	23.49 (5.12)	13.48 (3.69)	9.86 (2.76)	7.20 (1.99)	8.86 (2.25)	11.19 (3.01)	17.17 (4.76)
	Min-max	8.66-31.78	5.93-20.10	4.81-14.24	4.11-10.86	5.13-13.88	6.57-18.81	10.58-29.26

**p>0.05: Comparison of angles (A1-A7) between right and left tibiae **p<0.001: There was a significant difference in the comparison of the A1-A7, A2-A6, and A3-A5 parameters between the proximal and distal sagittal distances on both the right and left sides.*

does not provide detailed data on PTC [5]. In our study, the sagittal distances and angles of the posterior surface of the tibia are detailed for the proximal, median, and distal regions of the tibia.

A study comparing the curvature of the fibula diaphysis between the Jomon population, who were hunter-gatherers, and the modern Japanese population found that the fibula in modern individuals is significantly flatter [7]. This suggests that bone curvature is influenced by mechanical loading associated with daily activities.

Curvatures in long bones play a crucial role in managing bone stress and stiffness during skeletal loading. The axial forces and ground reaction forces from the muscles act around the longitudinal curvature of the bone, generating multidirectional bending moments [14]. It may be thought that the difference in curvature between the proximal and distal regions of the tibia may be due to the fact that the muscle insertions in the proximal region are more than those in the distal region, and the weight force components loaded on the bone are reflected more in the proximal region. Interventions involving the proximal tibia region can lead to misalignment, which may result in clinical problems due to tension on muscle tendons [14,15]. Misalignment can increase mechanical stress on the bone and lead to postoperative complications. Research on tibial morphology and curvature highlights the importance of accounting for proximal and distal variations during surgeries like total knee arthroplasty and intramedullary nailing to avoid complications such as cortical impingement and postoperative osteoarthritis [16]. Also, in total knee arthroplasty, selecting the correct entry point for the tibial alignment system is crucial because the tibial curvature and the axis of the intramedullary canal influence this entry point [17]. Therefore, we consider a thorough understanding of tibial morphometry essential for achieving optimal surgical outcomes.

In addition, the proper design of tibial prostheses, including alignment and stem insertion points, is essential for reducing stress on the bone and preventing complications like bone remodeling or implant loosening. Specifically, stem design for knee prostheses must consider tibial curvature and load distribution to avoid issues like strain shielding in the proximal tibia, which can affect postoperative outcomes [18]. For this reason, prostheses should also be designed by calculating these stresses. Accurate knowledge of tibial curvature and morphometry helps in selecting appropriate prosthetic designs that accommodate the natural biomechanics of the

https://doi.org/10.5455/annalsmedres.2024.12.261

tibia [19].

Our study could not be directly compared with previous studies due to differences in measurement methods and variables related to tibial curvature. Therefore, our data were evaluated independently. The main distinction of our study from others is the identification of regional variations in tibial curvature.

There are some limitations of this study. The number of bones available in our laboratory is limited; however, the aim of our study was to determine the difference in the curvature of the posterior border of the tibia in the proximal and distal regions as a preliminary study. The bones analyzed do not belong to the same individuals, and the lack of information on age and gender may affect the generalizability of the results.

CONCLUSION

In conclusion, this study highlights the importance of understanding tibial morphology and curvature when performing surgical procedures such as total knee arthroplasty and intramedullary nailing. Our findings demonstrate significant variations in PTC between the proximal and distal regions, which can influence the success of surgical outcomes. These variations, likely related to muscle insertions and biomechanical forces, underscore the need to account for tibial curvature when selecting prosthetic designs and surgical entry points. Future studies should aim to refine tibial morphometric data further to improve surgical precision and reduce postoperative complications.

Large-scale radiological studies are required to confirm the differences in posterior tibial curvature across genders, age groups, and populations, offering critical insights into its biomechanical and clinical implications.

Ethics Committee Approval: The study was approved by Izmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee (Decision No: 0312).

Informed Consent: As the study involved anonymized human skeletal remains with no associated personal data, informed consent was not applicable.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: M.K., N.A., M.A.M.; Design: M.K., N.A., M.A.M.; Supervision: M.A.M.; Materials: M.K.; Data Collection and/or Processing: M.K., N.A.; Analysis and/or Interpretation: M.K.; Literature Review: M.K.; Writing: M.K.; Critical Review: M.A.M.

Conflict of Interest: There is no conflict of interest.

Financial Disclosure: There is nothing to disclose.

REFERENCES

1. Bertram JE, Biewener AA. Bone curvature: sacrificing strength for load predictability? *J. Theor. Biol.* 1988;131(1):75-92. doi: 10.1016/s0022-5193(88)80122-x.
2. Shackelford LL, Trinkaus E. Late pleistocene human femoral diaphyseal curvature. *Am J Phys Anthropol.* 2002;118(4):359-70. doi: 10.1002/ajpa.10093.
3. Groote D, Elisabeth I, Maria P. A comprehensive analysis of long bone curvature in Neanderthals and modern humans using 3D morphometrics: University of London, University College London (United Kingdom); 2008.
4. De Groote I. Femoral curvature in Neanderthals and modern humans: a 3D geometric morphometric analysis. *J Hum Evol.* 2011;60(5):540-8. doi: 10.1016/j.jhevol.2010.09.009.
5. Macintosh AA, Davies TG, Pinhasi R, Stock JT. Declining tibial curvature parallels ∼6150 years of decreasing mobility in Central European agriculturalists. *Am J Phys Anthropol.* 2015;157(2):260-75. doi: 10.1002/ajpa.22710.
6. Tagomori H, Kaku N, Shimada T, Tsumura H. Effect of age and sex on femoral curvature in the Japanese population: three-dimensional computed tomography findings. *Anat Sci Int.* 2021;96(3):411-21. doi: 10.1007/s12565-021-00606-x.
7. Hagihara Y. Fibular diaphyseal curvature of the Jomon population. *Anat Sci Int.* 2023;98(4):548-57. doi: 10.1007/s12565-023-00722-w.
8. Lanyon LE. Functional strain in bone tissue as an objective, and controlling stimulus for adaptive bone remodelling. *J Biomech.* 1987;20(11-12):1083-93. doi: 10.1016/0021-9290(87)90026-1.
9. Imamura T, Ogami-Takamura K, Saiki K, Hamamoto A, Endo D, Murai K, et al. Morphological divergence in the curvature of human femoral diaphyses: Tracing the central mass distributions of cross-sections. *J Anat.* 2021;239(1):46-58. doi: 10.1111/joa.13399.
10. Lanyon L. The influence of function on the development of bone curvature. An experimental study on the rat tibia. *Journal of Zoology.* 1980;192(4):457-66. doi: 10.1111/j.1469-7998.1980.tb04243.x.
11. Cheema JI, Grissom LE, Harcke HT. Radiographic characteristics of lower-extremity bowing in children. Radiographics : a review publication of the Radiological Society of North America, Inc. *Radiographics.* 2003;23(4):871-80. doi: 10.1148/rg.234025149.
12. Zbinden I, Rutz E, Jacobson JA, Magerkurth O. Tibial bowing in children - what is normal? A radiographic study. *Eur Radiol.* 2015;25(12):3459-71. doi: 10.1007/s00330-015-3785-1.
13. Valcarenghi J, Vittone G, Mouton C, Coelho Leal A, Ibañez M, Hoffmann A, et al. A systematic approach to managing complications after proximal tibial osteotomies of the knee. *J Exp Orthop.* 2023;10(1):131. doi: 10.1186/s40634-023-00708-7.
14. Akdemir Aktaş H, Ülkir M, Günenç Beşer C, Demiryürek D. Reappraisal of the proximal tibia anatomy in Turkish population. *Surg Radiol Anat.* 2023;45(3):263-70. doi: 10.1007/s00276-023-03094-y.
15. Charng J-R, Chen AC-Y, Chan Y-S, Hsu KY, Wu C-T. Proximal tibial morphology and risk of posterior tibial cortex impingement in patients with AA-sized Oxford unicompartmental knee arthroplasty tibial implants. *J Orthop Surg Res.* 2020;15(1):380. doi: 10.1186/s13018-020-01900-6.
16. Biewener, A A. Locomotory stresses in the limb bones of two small mammals: the ground squirrel and chipmunk. *J Exp Biol.* 1983;103(1):131-54. doi: 10.1242/jeb.103.1.131.
17. Kwak DS, Han CW, Han SH. Tibial intramedullary canal axis and its influence on the intramedullary alignment system entry point in Koreans. *Anat Cell Biol.* 2010;43(3):260-7. doi: 10.5115/acb.2010.43.3.260.
18. Cawley DT, Kelly N, Simpkin A, Shannon FJ, McGarry JP. Full and surface tibial cementation in total knee arthroplasty: a biomechanical investigation of stress distribution and remodeling in the tibia. *Clin Biomech (Bristol).* 2012;27(4):390-7. doi: 10.1016/j.clinbiomech.2011.10.011.
19. Scott C, Biant L. The role of the design of tibial components and stems in knee replacement. *J Bone Joint Surg Br.* 2012;94(8):1009-15. doi: 10.1302/0301-620X.94B8.28289.

https://doi.org/10.5455/annalsmedres.2024.12.261

Ann Med Res

Current issue list available at Ann Med Res

Annals of Medical Research

journal page: annalsmedres.org

Prevalence of hypertension in asymptomatic children without risk factors

Pelin Arslan [a],*, Mehmet Tekin [a]

[a]Inonu University, Faculty of Medicine, Department of Pediatrics, Malatya, Türkiye
*Corresponding author: ptulun73546@gmail.com (Pelin Arslan)

MAIN POINTS

- The study found a total hypertension prevalence of 32.5
- Multiple regression analysis revealed that Body Mass Index (BMI), family history of hypertension, maternal obesity, and paternal coronary artery disease are significant independent risk factors for hypertension in this population.
- There was a positive correlation (r: 0.468, p<0.001) between BMI and hypertension detection, indicating that higher BMI is associated with increased hypertension risk, even in children without other known risk factors.
- The findings suggest that routine blood pressure screening for all children aged 3-18 years is essential, even in the absence of risk factors, to prevent future cardiovascular issues.

Cite this article as: Arslan P, Tekin M. Prevalence of hypertension in asymptomatic children without risk factors. *Ann Med Res*. 2025;32(5):180–186. doi: 10.5455/annalsmedres.2024.12.279.

ABSTRACT

Aim: This two-year a cross-sectional study investigated the prevalence of hypertension in asymptomatic children (ages 3-18) without known risk factors, hypothesizing that increased screen time and sedentary lifestyles contribute to rising rates. The cross-sectional study, conducted from January 1, 2021, to January 1, 2022, included children attending the General Pediatrics clinic at İnönü University Faculty of Medicine.

Materials and Methods: Of the 468 participants, 10.3% had prehypertension, 15.2% had stage 1 hypertension, and 7.1% had stage 2 hypertension, resulting in a total hypertension prevalence of 32.5%. The hypertensive group had a significantly higher BMI (19.3±5.4 vs. 17.6±3.6, p<0.001). Paternal coronary artery disease was less prevalent in the hypertensive group (2.6% vs. 7.9%, p=0.038), while maternal obesity was more prevalent (14.4% vs. 6.0%, p=0.003). Spearman's correlation showed a positive association between BMI and hypertension (r: 0.468, p<0.001).

Results: Multiple regression analysis identified BMI (OR 1.154; p<0.001), family history of hypertension (OR 1.543, p=0.040), paternal coronary artery disease (OR 0.282, p=0.026), and maternal obesity (OR 2.238, p=0.022) as independent risk factors. This translates to a 1.154- fold increased risk of hypertension with higher BMI, a 1.543-fold increased risk with a family history, a protective effect (0.282-fold) with paternal coronary artery disease, and a 2.238-fold increased risk with maternal obesity.

Conclusion: This study found a higher prevalence of hypertension than previous research, likely due to the inclusion of prehypertension and stage 1 hypertension. Despite excluding obese children, hypertension correlated with increasing BMI, and family history, paternal coronary artery disease, and maternal obesity were independent predictors. Given the rising prevalence of childhood hypertension, blood pressure measurement is recommended for all 3-18-year-olds, even without known risk factors.

Keywords: Hypertension, Coronary artery disease, Obesity, Body mass index

Received: Jan 03, 2025 **Accepted:** Apr 09, 2025 **Available Online:** May 26, 2025

INTRODUCTION

According to both the American Academy of Pediatrics (AAP) and the European Society of Hypertension guidelines, normal blood pressure (BP) is defined as BP values lower than the 90th percentile based on age, gender, and height [1, 2]. Before puberty, "prehypertension" was defined as systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) ≥90th percentile and <95th percentile (according to age, gender, and height tables). For adolescents, "prehypertension" was defined as BP ≥120/80 mm Hg and <95th percentile, or ≥90th and <95th percentile (whichever is lower) [1]. Hypertension (HT) is defined as clinically measured mean SBP and/or DBP ≥95th percentile (based on age, gender, and height percentiles) [1]. It is also classified as stage 1 HT (≥95th percentile) and stage 2 HT (≥95th percentile + 12 mm Hg) [1].

Although hypertension is less common in children under 18 years of age, its prevalence is gradually increasing. According to the Infant, Child, and Adolescent Monitoring Protocols (ICAP) of the Public Health Institution of Turkey, Ministry of Health, it is reported that the prevalence of high blood pressure is 1-3% throughout childhood, but the prevalence of hypertension is around 5%, in parallel with the increasing prevalence of obesity in adolescents [3]. In a study conducted in our country in 2013, the prevalence of hypertension in chil-

https://doi.org/10.5455/annalsmedres.2024.12.279

dren aged 5-18 years was found to be 6.1% [4]. It can be said that the prevalence of hypertension in childhood is increasing in our country as well as globally. Over the 15 years from 2000 to 2015, it was found that the prevalence of childhood hypertension increased, with the rates of increase being similar across all age ranges. Recent studies show the prevalence of hypertension as 4.32% in six-year-old children and 7.89% in 14-year-old children [5]. Clinical guidelines recommend the inclusion of routine blood pressure measurement in the health monitoring of children aged 3 years and above [1]. Screenings are useful for the early recognition of asymptomatic hypertension. The timely identification of abnormal blood pressure values in pediatric and adolescent populations is essential for mitigating the risk of cardiovascular disease and mortality later in life.

We hypothesize that altered eating patterns and reduced physical activity due to increased screen time may be contributing to the rising prevalence of hypertension in the pediatric population. Accordingly, our study aimed to determine the prevalence of hypertension in asymptomatic children aged 3–18 years without identifiable risk factors.

MATERIALS AND METHODS

Patients included in the study

Between January 1, 2021, and January 1, 2022, a cross-sectional study was conducted; including children aged 3 to 18 years who had no identified risk factors for high blood pressure. The number of patients who had their blood pressure measured during their first visit is as follows. Blood pressure measurements were taken for each patient during their initial application. These children were seen at the pediatric general outpatient clinic of İnönü University's Faculty of Medicine. Written informed consent was obtained from the participants and their families after a thorough explanation of the study.

Definitions

Hypertension was diagnosed as a blood pressure value above the 95th percentile based on age, gender, and height percentiles, or a value higher than 130/80 mmHg [1]. A standardized blood pressure measurement procedure was followed for all patients attending the outpatient clinic: measurements were taken on the right arm at heart level, after at least five minutes of rest. The patient's back was supported, feet were flat on the ground, and no impediments to accurate measurement were present. The first sound heard over the brachial artery while slowly releasing the cuff pressure during auscultatory blood pressure measurement (Korotkoff phase 1) was accepted as systolic blood pressure (SBP), and the moment when the sounds completely disappeared (Korotkoff phase 5) was accepted as diastolic blood pressure (DBP) [6,7,8].

Overweight and obesity were defined according to the Centers for Disease Control (CDC, 2000) criteria. According to the body mass index (BMI) percentile tables, a BMI at or above the 85th percentile was classified as overweight, and a BMI at or above the 95th percentile was classified as obese [5]. Height and weight percentiles, based on age and gender, were determined using growth curves prepared for Turkish children [6]. Participants in this study were children aged 3 to 18 years who attended the general pediatrics outpatient department and had no established risk factors for hypertension.

Data collection

The following variables were recorded for each participant: age, gender, weight, BMI, blood pressure percentile, history of hypertension in parents, hypertension in other family members, coronary disease in parents, coronary disease in other family members, renal disease in parents, renal disease in other family members, obesity in parents, and obesity in other family members.

Exclusion criteria

- History of previously diagnosed hypertension
- History of preterm birth, low birth weight, or hospitalization in a neonatal care unit
- Use of medications that may increase blood pressure, including antihypertensive drugs
- Presence of conditions such as diabetes mellitus, hyperlipidemia, obesity, congenital heart disease, recurrent urinary tract infections, kidney disease, or anomalies that may lead to increased intracranial pressure and hypertension
- Chronic diseases such as organ transplantation or malignancy
- Obesity (defined as a BMI >95th percentile)
- Patients with a history of hypertension or cardiovascular disease in a first-degree relative were excluded from the study.

Power analysis

In the power analysis conducted to evaluate the prevalence of hypertension in asymptomatic children without risk factors, we determined that the minimum required sample size was 450. This calculation was based on an alpha margin of error of 0.05, an effect size of 0.15, power of 0.95, and a critical t-value of 1.64.

Statistical analysis

Data analysis was performed using IBM SPSS Version 22.0 (Armonk, NY: IBM Corp.). Continuous data were summarized using mean and standard deviation or median and range, whereas categorical data were presented as counts (n) and proportions (%), along with the median and interquartile range (IQR), representing the 25th and 75th percentiles. Chi-square

https://doi.org/10.5455/annalsmedres.2024.12.279

analysis (Pearson Chi-square) was used to compare categorical variables between the groups, and the normality of continuous variables was assessed using the Shapiro-Wilks Test. Independent Samples t-test was employed to compare continuous variables conforming to normal distribution between the two groups. The Spearman correlation test was used to evaluate the correlation between body mass index (BMI) and hypertension detection. Multiple binary logistic regression analysis (Backward LR model) was applied to determine the independent risk factors for hypertension. A p-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

The study ultimately included 468 children (220 females [47%] and 248 males [53%]) after excluding 32 participants from the initial cohort of 500. Exclusions were made due to subsequent diagnoses of chronic diseases (n=10), incomplete data (n=20), and recurrent urinary tract infections (n=2).

As shown in Table 1, the median age of the participants was 9 years (range: 2 years to 17 years). The median body weight was 33.5 kg (range: 11.5 kg to 88.0 kg). The median BMI was 17.05 (range: 1.0 to 36.6).

Regarding family medical history, 29 (6.2%) children's mothers, 38 (8.1%) children's fathers, and 233 (49.3%) children had a diagnosis of hypertension (HT). Additionally, 24 (5.1%) children's mothers, 29 (6.2%) children's fathers, and 197 (42.7%) children had a history of coronary artery disease (CAD). Furthermore, 8 (1.7%) children's mothers, 14 (3.0%) children's fathers, and 102 (21.8%) children had a history of kidney disease. Finally, 41 (8.8%) children's mothers, 32 (6.6%) children's fathers, and 120 (25.6%) children's family members (other than first-degree relatives) were diagnosed with obesity (Table 1).

Table 1. Demographic data of the patients included in the study.

	Frequency (n %)
Age (years) (min. - max.)	9 (3 - 17)
Body Weight (min. - max.)	33.5 (11.5 -- 88.0)
Body Mass Index (min. - max.)	17.05 (1.0 -- 36.6)
Maternal HT	29 (6.2)
Paternal HT	38 (8.1)
Family HT	233 (49.3)
Maternal coronary artery disease	24 (5.1)
Paternal history of coronary artery disease	29 (6.2)
Family history of coronary artery disease	197 (42.7)
Maternal Kidney Disease	8 (1.7)
Paternal Kidney Disease	14 (3.0)
Family history of kidney disease	102 (21.8)
Maternal Obesity	41 (8.8)
Paternal Obesity	32 (6.6)
Obesity in the Family	120 (25.6)

Table 2. Classification of cases according to blood pressure measurement.

Blood pressure	Frequency (n %)
Normal blood pressure	316 (67.5)
Pre-HT	48 (10.3)
Stage 1	71 (15.2)
Stage 2	33 (7.1)

Of the 468 children included in the study, 316 (67.5%) had normal blood pressure, 48 (10.3%) had prehypertension, 71 (15.2%) had stage 1 HT, and 33 (7.1%) had stage 2 HT (Table 2). The overall prevalence of hypertension in our study group was calculated to be 32.5%.

The mean age was 9.1 ± 4.1 years in the hypertensive group and 9.9 ± 4.2 years in the non- hypertensive group (p = 0.044). However, a statistically significant difference was observed in body mass index (BMI), with the hypertensive group exhibiting a mean of 19.3 ± 5.4 compared to 17.6 ± 3.6 in the non-hypertensive group (p < 0.001). A history of hypertension (HT) in family members other than first-degree relatives was present in 86 (56.6%) patients in the hypertensive group and 147 (46.5%) children in the non-hypertensive group (p = 0.048).

The fathers of 4 (2.6%) patients in the hypertensive group had a history of coronary artery disease (CAD), while the fathers of 25 (7.9%) children in the non-hypertensive group had a history of CAD (p = 0.038). The mothers of 22 (14.4%) children in the hypertensive group had a history of obesity, whereas the mothers of 19 (6.0%) children in the non-hypertensive group had a history of obesity (p = 0.003). A statistically significant difference was observed in the presence of maternal obesity between the two groups, with a higher proportion found in the hypertensive group (Table 3).

Spearman's correlation test performed to determine the correlation between body mass index and HT detection revealed a positive correlation between BMI and HT detection (r: 0.468 p<0.001) (Table 4).

In the binary multiple regression analysis (Backward LR model), the following were identified as independent risk factors for hypertension in children: body mass index (OR 1.154; p<0.001), a history of hypertension in family members other than first-degree relatives (OR 1.543, p = 0.040), a history of coronary artery disease in the father (OR 0.282, p = 0.026), and the presence of obesity in the mother (OR 2.238, p = 0.022) (Table 5).

According to these results, the risk of hypertension increased by 1.154-fold for higher body mass index, 1.543-fold for a family history of hypertension, 0.282-fold for a father's history of coronary artery disease, and 2.238-fold for maternal obesity. Furthermore, younger age appeared to increase the risk of hypertension by 0.884-fold.

DISCUSSION

Hypertension is a significant health issue that contributes to a high number of deaths worldwide each year [9]. An increasing number of studies suggest that the causes of hypertension seen in adults often begin in childhood. Since childhood hy-

https://doi.org/10.5455/annalsmedres.2024.12.279

Table 3. Comparison of demographic characteristics between the hypertension and non- hypertension groups.

	Group with hypertension (n=152) (n, %)	Group without hypertension (n=316) (n, %)	p
Gender (female/male)[a]	72/80	148/168	0.922
Age (years)[b]	9.1±4.1	9.9±4.2	0.044*
Body Weight (kg)[b]	38.0±19.0	36.3±16.5	0.323
Body Mass Index[b]	19.3±5.4	17.6±3.6	<0.001*
Maternal HT[a]	12 (7.8)	17 (5.3)	0.309
Paternal HT[a]	10 (6.5)	28 (8.8)	0.472
Family HT[§]	86 (56.6)	147(46.5)	0.048*
Maternal coronary artery disease[a]	9 (5.9)	15 (4.7)	0.656
Paternal history of coronary artery disease[a]	4 (2.6)	25 (7.9)	0.038*
Family history of coronary artery disease[a§]	1 (0.6)	0 (0.0)	0.163
Maternal Kidney Disease[a]	2 (1.3)	6 (1.8)	0.728
Paternal Kidney Disease[a]	3 (1.9)	10 (3.1)	0.410
Family history of kidney disease[a§]	28 (18.4)	74 (23.4)	0.234
Maternal Obesity[a]	22 (14.4)	19 (6.0)	0.003*
Paternal Obesity[a]	12 (7.8)	19 (6.0)	0.552
Obesity in the Family[a§]	43 (28.2)	77 (24.3)	0.368

**p<0.05;, Pearson Chi-square test (number, %): , Independent Student T test (meanSD) , Family assessment includes family members other than mother and father.*

Table 4. Correlation between body mass index and hypertension.

	r	p
BMI- Hypertension	0.468	<0.001*

pertension is a known risk factor for renal diseases, cardiovascular conditions, and cerebrovascular diseases in adulthood, early diagnosis and management are crucial [10]. Although hypertension is less common in children than in adults, diagnosing it can be challenging. This study aimed to examine the current prevalence of hypertension in children aged 3-18 years who have no known risk factors.

A study conducted in China in 2018 found that the prevalence of prehypertension was 6% among children aged 7-15 years [10]. In a 2017 report by Larkins et al. in Australia, the prevalence of hypertension in children aged 2-17 years was reported as 15.6%, while the prevalence of prehypertension was 12.3% [11]. Similarly, a 2010 study in Turkey reported a 7% hypertension prevalence among 1,963 children aged 7-16 years [12]. The lower figure in this study may be attributed to the exclusion of prehypertension and stage 1 hypertension.

In our study, which included 468 children, the following distribution was observed: normal blood pressure in 316 children (67.5%), prehypertension in 48 children (10.3%), stage 1 hypertension in 71 children (15.2%), and stage 2 hypertension in 33 children (7.1%). Thus, the total prevalence of hypertension in our study group was calculated to be 32.5%. This figure is higher compared to previous studies, which can be attributed to the inclusion of prehypertension and stage 1 hypertension in our analysis. This highlights the importance of considering these stages for a more accurate estimation of hypertension prevalence in asymptomatic children without identified risk factors.

Different results have been reported in studies investigating the relationship between hypertension and gender in children. While many studies have shown no significant association with gender, others conducted in various geographical regions and among different ethnic groups have found that hypertension is more common in males [13]. A study by M. Kaplan, conducted at Istanbul University with 349 hypertensive patients, reported a higher prevalence of hypertension in males (58.2%), but this difference did not reach statistical significance [14]. Similarly, a 2015 study by Yücel and Toprak found no significant gender-based differences in hypertension prevalence [15]. In our study, 72 (15.38%) of the hypertensive patients were female, while 80 (17.09%) were male, and this difference was not statistically significant.

Growth and development are directly related to blood pressure. It is known that blood pressure increases linearly in children between the ages of 1 and 3 years, likely due to body development rather than age alone. The differing growth patterns between boys and girls as they mature also lead to corresponding changes in blood pressure levels. In children under six years of age, blood pressure levels tend to be similar between the sexes. However, research suggests that girls experience a more rapid increase in blood pressure during the 6-11 year age range compared to the 11-17 year age range, while boys show a more pronounced rise in blood pressure between the ages of 12 and 17 [16,17].

Bachmann et al., in a study conducted with 1,165 subjects aged 4-18 years in the Essen region of Germany, found that blood pressure increased with age, and adolescent boys had higher blood pressure compared to preadolescent boys and adolescent girls [18]. Similarly, Akış et al. [19] found a positive association between age and hypertension. However, our study revealed a different trend: the mean age of the hypertensive group (9.1 ± 4.1 years) was lower than the mean age of the normotensive group (9.9 ± 4.2 years). We hypothesize that

https://doi.org/10.5455/annalsmedres.2024.12.279

Table 5. Determination of independent risk factors increasing the risk of hypertension detection in children by multiple logistic regression analysis.

	Beta	OR	%95 CI	p
Body Mass Index	0.144	1.154	1.089 -- 1.224	<0.001*
History of hypertension in family members other than first degree	0.433	1.543	1.020 -- 2.333	0.040*
Paternal history of coronary artery disease	-1.267	0.282	0.092 -- 0.861	0.026*
Maternal obesity	0.806	2.238	1.121 -- 4.467	0.022*

**p<0.05; OR, odds ratio; 95% CI, confidence interval.*

the significantly lower mean age in the hypertensive group was due to the exclusion of obese children from the study. As is well known, obesity is more prevalent in adolescents.

In recent years, the increase in the prevalence of obesity, the consumption of high-calorie, fatty, and salty foods, decreased physical activity, and increased stress have contributed to the rising prevalence of hypertension [20]. It has been reported that the prevalence of obesity has increased by approximately 40% in the last 40 years [16]. In a study by Fuiano et al., which measured blood pressure three times in 1,563 schoolchildren aged 3-16 years, obesity was found in 23% of boys and 31.2% of girls whose blood pressure exceeded the 95th percentile [21]. These values were significantly higher than those in children with normal blood pressure, and obesity was identified as a risk factor for hypertension. Similarly, Akış et al. found a correlation between weight gain and hypertension in a study involving 2,478 school- aged children aged 12-14 years in Bursa Province [22]. In their study, excess weight was found to significantly increase the frequency of hypertension.

In our study, the body mass index (BMI) of the hypertensive group was 19.3 ± 5.4, compared to 17.6 ± 3.6 in the normotensive group. The BMI was statistically significantly higher in the hypertensive group compared to the normotensive group. Although we did not include obese patients in our study, the BMI was found to be higher in the hypertensive group, which further supports the relationship between weight gain and the prevalence of hypertension.

Additionally, a positive correlation was observed between BMI and the detection of hypertension. These findings reinforce the established link between excess weight and increased risk of hypertension.

A family history of hypertension is considered an important risk factor for the development of hypertension in both childhood and adulthood [23]. In a study by Bryl et al., which examined 86 children diagnosed with primary hypertension, 39% had a history of hypertension in their fathers and 27% in their mothers [24]. Similarly, a retrospective study by Robinson et al. found that 49% of the parents of children with primary hypertension had hypertension, while 10% had secondary hypertension [23]. In a study by Akış et al., the prevalence of hypertension was 4.9% in children without a family history of hypertension, whereas it was 10.9% in children with a family history of hypertension [19]. Additionally, Anand and Tandon found that in children aged 5-17 years, the prevalence of hypertension was 5.9% in those with a family history of hypertension and 0.14% in those without [25].

In our study, when examining family history, 7.8% of children in the hypertensive group had a history of hypertension in their mothers, compared to 5.3% in the normotensive group. Likewise, 6.5% of children in the hypertensive group had a history of hypertension in their fathers, while 7.9% of the children in the normotensive group had a family history of hypertension in their fathers. Notably, 56.6% of the non-first-degree family members of hypertensive children had a history of hypertension, compared to 46.5% in the group without hypertension. Although there was no significant difference between the two groups in terms of hypertension prevalence in parents, the family history of hypertension in extended family members (outside of the first degree) was significantly higher in the hypertensive group. This finding is consistent with the literature, which emphasizes the role of family history in the development of childhood hypertension.

Gupta et al. conducted a study in 3194 children aged 5-15 years, finding that the presence of a family history of coronary heart disease (CAD) was significantly lower in the families of children with normal blood pressure compared to those with hypertension [25]. In our study, the mothers of 9 children in the hypertensive group had a history of CAD, while the mothers of 15 children in the normotensive group had a history of CAD. Similarly, the fathers of 4 children in the hypertensive group had a history of CAD, compared to 25 fathers in the normotensive group. Consistent with previous studies, our findings suggest that a history of CAD in fathers was more prevalent in children with hypertension.

Renal diseases are among the most common causes of secondary hypertension in children. In developing countries, consanguineous marriages contribute to an increased frequency of hereditary kidney diseases, such as polycystic kidney disease [26]. In our study, the mothers of two children in the hypertensive group had a history of renal disease, compared to six mothers in the normotensive group. The fathers of three children in the hypertensive group had a history of renal disease, while ten fathers in the normotensive group had a history of renal disease. When considering the entire family, 28 patients in the hypertensive group had a family history of kidney disease, compared to 74 patients in the normotensive group. Since we excluded children with chronic diseases or recurrent urinary tract infections from our study, no significant

https://doi.org/10.5455/annalsmedres.2024.12.279

difference was observed between the two groups in terms of family history of kidney disease.

In a study conducted in Canada with 15,245 participants, it was reported that the likelihood of obesity in relatives was five times higher when familial risk was considered, compared to the general Canadian population [27]. Similarly, a study titled "Renal functions and inflammation markers in healthy obese school children," conducted in Adana, found that the obesity rate in the parents of obese children was significantly higher compared to the control group [28]. Furthermore, it has been shown that if both parents are obese, the likelihood of their children becoming overweight between the ages of 3 and 10 years exceeds 75%. In contrast, this probability drops to 25-50% if only one parent is obese [8]. In our study, when evaluating the families of children with hypertension, a history of maternal obesity was present in 22 children in the hypertensive group, compared to 19 children in the normotensive group. The presence of maternal obesity was statistically significantly higher in the hypertensive group. Additionally, 12 fathers in the hypertensive group had a history of obesity, while 19 fathers in the normotensive group had a history of obesity. Moreover, 43 children in the hypertensive group had a family history of obesity in relatives beyond the first degree, compared to 77 children in the normotensive group.

Limitations

The exclusion of obese patients, who are already known to have a risk factor for hypertension, strengthens the validity of our study in determining the true prevalence of hypertension (HT) in children without risk factors. This study is hospital-based, which limits its ability to be generalized to the broader population. The inclusion of patients from a single hospital may not fully represent the entire pediatric population. Additionally, the relatively small sample size further restricts the generalizability of our findings.

CONCLUSION

In conclusion, the prevalence of HT in our study was higher compared to previous studies. We believe this result is due to the inclusion of prehypertension and stage 1 HT in our study. Although we excluded obese children, we found a correlation between increasing body mass index (BMI) and the prevalence of HT. Additionally, a family history of HT, coronary artery disease (CAD) in the father, and maternal obesity were identified as independent predictors of HT in children. Given the rising prevalence of HT in children, we recommend that blood pressure be measured during physical examinations for all patients aged 3–18 years, even in those without apparent risk factors. To further strengthen our findings, future studies should involve larger patient cohorts, including those from primary care centers.

Ethics Committee Approval: Our study was approved by the İnönü University Faculty of Medicine, Health Sciences Non-Interventional Clinical Research Ethics Committee on October 15, 2020 (Approval No. 27942812-770). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from the participants and their families after a thorough explanation of the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest for authors.

Financial Disclosure: None.

REFERENCES

1. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017 Sep;140(3):e20171904. doi: 10.1542/peds.2017-1904. Epub 2017 Aug 21.
2. Lurbe E, Cifkova R, Cruickshank JK, et al. Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. *J Hypertens.* 2009;27(9):1719–42. doi: 10.1097/hjh.0b013e32832f4f6b.
3. Kural B. Sağlam Çocuk İzleminde Hipertansiyon Taraması. *Çocuk Dergisi.* 2019;19(2):60–62. doi:10.5222/j.child.2019.45403.
4. Duzova A, Yalcinkaya F, Baskin E, Bakkaloğlu A, Soylemezoglu O (2013) Prevalence of hypertension and decreased glomerular filtration rate in obese children: results of a population-based field study. *Nephrol Dial Transplant.* 2013;28:166–71. doi: 10.1093/ndt/gft317.
5. Song P, Zhang Y, Yu J, et al. Global prevalence of hypertension in children: a systematic review and meta-analysis. *JAMA Pediatr.* 2019;173(12):1154–63. doi: 10.1001/jamapediatrics.2019.3310.
6. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004;114(2 Suppl 4th Report):555-76. PMID: 15286277.
7. Lurbe E, Agabiti-Rosei E, Cruickshank JK, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens.* 2016;34(10):1887–1920. doi: 10.1097/HJH.0000000000001039.
8. Paskalev D, Kircheva A, Krivoshiev S. A centenary of auscultatory blood pressure measurement: a tribute to Nikolai Korotkoff. *Kidney Blood Press Res.* 2005;28(4):259–63. doi: 10.1159/000090084.
9. Peterson CG, Miyashita Y. The use of ambulatory blood pressure monitoring as standard of care in pediatrics. *Front Pediatr.* 2017;5:153. doi: 10.3389/fped.2017.00153.
10. Lu Y, et al. Prevalence of hypertension and prehypertension and its association with anthropometrics among children: a cross-sectional survey in Tianjin, China. *J Hum Hypertens.* 2018;32(11):789–98. doi: 10.1038/s41371-018-0088-4.
11. Larkins N, Teixeira-Pinto A, Banks E, et al. Blood pressure among Australian Aboriginal children. *J Hypertens.* 2017 Sep;35(9):1801–7. doi: 10.1097/HJH.0000000000001401.
12. Akgun C, Dogan M, Akbayram S, et al. The incidence of asymptomatic hypertension in school children. *J Nippon Med Sch.* 2010 Jun;77(3):160–165. doi: 10.1272/jnms.77.160.
13. Kit BK, Kuklina E, Carroll MD, et al. Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999-2012. *JAMA Pediatr.* 2015;169(3):272–9. doi: 10.1001/jamapediatrics.2014.3216.
14. Kaplan MM, Yıldırım ZY, Aksu BY, et al. Çocuklarda hipertansiyon etiyolojisi ile yaşam içi kan basıncı izlemi arasındaki ilişki. *J Child.* 2018;18(3):121–128. doi: 10.5222/j.child.2018.60465.

https://doi.org/10.5455/annalsmedres.2024.12.279

15. Yücel BB, Toprak D. 6-16 yaş arası obez çocuklarda antropometrik ölçümlerin ve biyokimyasal parametrelerin değerlendirilmesi. *Ankara Med J.* 2016;16(1) doi: 10.17098/amj.90827.
16. Buyan N. Çocukluk çağı hipertansiyonu. *Turk Klinikleri Pediatrik Bilimler-Özel Konular.* 2008;4(1):72–93.
17. Ün M, Yegül S, Çoşanay B, et al. Çocuk ve Hastane. *Nobel Akademik Yayıncılık.*
18. Bachmann H, Horacek U, Leowsky M, et al. Blood pressure in children and adolescents aged 4 to 18. Correlation of blood pressure values with age, sex, body height, body weight and skinfold thickness (Essen Blood Pressure Study). *Monatsschr Kinderheilkd.* 1987;135(3):128–134. PMID: 3587234.
19. Akis N, Pala K, Irgil E, et al. Prevalence and risk factors of hypertension among schoolchildren aged 12-14 years in Bursa, Turkey. S*audi Med J*. 2007;28(8):1263–8. PMID: 17676215.
20. Manzoli L, Ripari P, Rotolo S, et al. Prevalence of obesity, overweight, and hypertension in children and adolescents from Abruzzo, Italy. *Ann Ig.* 2005;17(5):419–31. PMID: 16353679.
21. Fuiano N. Overweight and HT longitudinal study in school-aged children. *Minerva Pediatr.* 2006;58(5):451–459. PMID: 17008856.
22. Akış N, Pala K, İrgil E, et al. Bursa ili Orhangazi ilçesi 6 merkez ilköğretim okulunda 6- 14 yaş grubu öğrencilerde kilo fazlalığı ve obezite. *Uludağ Univ Tip Fak Derg*. 2003;29(3):17–20.
23. Flynn JT, Alderman MH. Characteristics of children with primary hypertension seen at a referral center. *Pediatr Nephrol.* 2005;20(7):961–6. doi: 10.1007/s00467-005-1855-3.
24. Bryl W, Miczke A, Cymerys M, et al. PO16-428 Prevalence of risk factors in children and youth with primary hypertension. *Atherosclerosis Suppl.* 2007;8(1):122. doi: 10.1016/S1567-5688(07)71438-1.
25. Gupta AK. Influence of family history of morbid cardiovascular events on blood pressure levels of school children. *Indian Pediatr.* 1991;28(2):131–9.
26. Smellie JM, Prescod NP, Shaw PJ, et al. Childhood reflux and urinary infection: a follow- up of 10–41 years in 226 adults. *Pediatr Nephrol.* 1998;12:727–36. PMID: 2055627.
27. Katzmarzyk PT, Perusse L, Rao DC, et al. Familial risk of obesity and central adipose tissue distribution in the general Canadian population. *Am J Epidemiol.* 1999;149(10):933– 42. doi: 10.1093/oxfordjournals.aje.a009737.
28. Cındık N, Baskın E, Ağras PI, et al. Sağlıklı şişman okul çocuklarında böbrek fonksiyonları ve enflamasyon belirteçleri. *Çocuk Sağlığı ve Hastalıkları Derg.* 2006;49(1):24– 29.
29. Zinner SH, Rosner BERNARD, Oh WILLIAM, et al. Significance of blood pressure in infancy. Familial aggregation and predictive effect on later blood pressure. *Hypertension.* 1985;7(3 Pt 1):411–16. PMID: 3997223.
30. Jobbágy Á, Csordás P, Mersich A. Blood pressure measurement: assessment of a variable quantity. *Zdravn Vestn*. 2011;80(4).

https://doi.org/10.5455/annalsmedres.2024.12.279

Ann Med Res

Current issue list available at Ann Med Res

Annals of Medical Research

journal page: annalsmedres.org

Obstetric and neonatal outcomes in pregnant women with anxiety disorders

Betul Akgun Aktas [a],*, Dilek Sahin [a]

[a] *Turkish Ministry of Health, Ankara Bilkent City Hospital, Department of Obstetrics and Gynecology, Division of Perinatology, Ankara, Türkiye*

**Corresponding author: Betul Akgun Aktas (drbetul07@gmail.com)*

MAIN POINTS

- Psychological distress in the mother has a negative effect on the fetus.
- There has been a marked increase in the prevalence of anxiety disorders in Turkey in recent years.
- Anxiety disorders are associated with adverse obstetric outcomes.

Cite this article as: Akgun Aktas B, Sahin D. Obstetric and neonatal outcomes in pregnant women with anxiety disorders. *Ann Med Res*. 2025;32(5):187–191. doi: 10.5455/annalsmedres.2025.01.026.

ABSTRACT

Aim: To examine the obstetric and neonatal prognoses of women with pregestational anxiety and contribute to maternal and neonatal health for pregnant women managing anxiety.

Materials and Methods: This retrospective study included 60 women with singleton pregnancies aged between 18 and 45 years who presented to the Perinatology Clinic of Ankara City Hospital between January 1, 2021, and December 1, 2024, and were diagnosed with anxiety disorders in the psychiatry department of the same hospital during the prenatal period. We evaluated the demographic characteristics such as age and gravidity, and clinical factors such as obstetric complications, birth weight, first- and fifth-minute Apgar scores, and neonatal intensive care requirements.

Results: The median age of pregnant women monitored for anxiety disorders was 31 years. Generalized anxiety disorder was the most common diagnosis among the anxiety disorders. Medical treatment was administered to 60% of the pregnant women. Of the patients diagnosed with anxiety disorders, 12 experienced preterm delivery. Five patients were diagnosed with hypertensive disorders of pregnancy, and one patient with substance-induced anxiety disorder underwent emergency delivery due to placental abruption. Fetal anomalies observed in the study group included cataract (n=1), microcephaly (n=1), ileal atresia (n=1), and agenesis of the corpus callosum (n=1). Among newborns delivered by mothers with anxiety disorders, the median gestational age at birth was 38 weeks, and the median birth weight was 3000 grams.

Conclusion: Anxiety disorders are associated with adverse obstetric outcomes, particularly preterm delivery.

Keywords: Anxiety, Panic disorder, Maternal factors, Fetal factors, Obstetrics, Fetal anomaly

Received: Jan 21, 2025 **Accepted:** Apr 14, 2025 **Available Online:** May 26, 2025

INTRODUCTION

According to the World Health Organization, the prevalence of anxiety disorders (AD) is approximately 4%; however, only one in four individuals suffering from this condition receives treatment [1]. In Turkey, the Ministry of Health reports a 22.9% increase in anxiety disorders in recent years, with a higher prevalence among women [2]. The chronic stress environment created by this psychiatric condition, along with neurochemical changes in the central nervous system, eating disorders, and coagulation abnormalities caused by elevated cortisol levels, may lead to adverse maternal and fetal outcomes during pregnancy [3]. This study aimed to investigate the obstetric and neonatal prognoses of women with pregestational anxiety and contribute to maternal and neonatal health among pregnant women managing anxiety.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board (IRB) for scientific ethical conduct (IRB approval number: TABED 2-24-644). The study included women aged 18-45 with singleton pregnancies who visited Ankara City Hospital's Perinatology Clinic between January 2021 and December 2024 and were diagnosed with anxiety disorders during the prenatal period.

Anxiety, as defined in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) by the American Psychiatric Association, is characterized by persistent and excessive worry or anxiety about various activities for

at least six months. AD symptoms include restlessness, difficulty concentrating, fatigue, irritability, muscle tension, and sleep disturbances, with at least three of these six symptoms being present. Subcategories of anxiety disorders include generalized anxiety disorder, social phobia, panic disorder, separation anxiety disorder, mutism, and substance-induced anxiety.

The exclusion criteria for this study were pregnant women who were not evaluated by the department of psychiatry, those with confirmed fetal structural or chromosomal anomalies, who underwent high-risk prenatal screening tests and invasive procedures, and multiple pregnancies. We evaluated demographic characteristics such as age and gravidity and clinical characteristics such as obstetric complications, birth weight, first- and fifth-minute Apgar scores, and neonatal intensive care unit (NICU) admissions were evaluated.

Statistical analysis

The data were analyzed using IBM Statistical software Package for Social Sciences (SPSS)for Windows, Version 23.0 (Armonk, NY: IBM Corp.). The Shapiro-Wilk test was used to evaluate normality. Contiuous variables are expressed as medians and range (minimum-maximum values). The categorical variables were expressed as number of affected individuals and the percentage of the study population. This retrospective study included all patients diagnosed with anxiety disorder over the past four years, reflecting the entire eligible population rather than a sample size determined by a priori power analysis.

RESULTS

This study included 60 pregnancies diagnosed with AD based on DSM-IV criteria and followed up during pregnancy. The demographic characteristics of the study population are summarized in Table 1. The median age of the pregnant women evaluated for AD was 31 (range: 19–45) years. Among the participants, 19 (31.6%) were nulliparous, and 14 (23.3%) were single mothers. A total of 20 participants (33.3%) had chronic illnesses, with the most common being asthma in seven patients (11.6%) and chronic hypertension in six (10%).

Table 1. Demographic data of the participants.

	n = 60
Maternal age (years)	31 (19--45)
Gravity	2 (1-6)
Parity	1 (0-5)
Nulliparity (n, %)	19 (31.6)
Single mothers (n, %)	14 (23.3)
Chronic disease (n, %)	20 (33.3)
Mental disorder (n, %)	3 (0.05)
Smoking (n, %)	7 (11.6)

Note: Data given as median (Range: minimum–maximum) or number of affected individuals (percentage of the study populations).

Table 2. Psychiatric and medical history of the study group.

	n = 60
Generalized anxiety disorder	36 (0.60)
Panic disorder	19 (31.6)
Substance/medication-induced anxiety disorders	5 (0.08)
Medical treatment medication	36 (0.60)
Suicidal intentios	7 (11.6)

Note: Data given as number of affected individuals (percentage of the study population).

Table 3. Outcomes of the patients regrading pregnancy and birth outcomes of in the study group.

	n = 60
Obstetric complications (n, %)	
Preterm labor	12 (20)
High blood pressure	5 (0.08)
Diabetes	2 (0.03)
Fetal growth restriction	1 (0.01)
Gestational age at birth (week)	38 (31-40)
Emergency cesarean delivery (n, %)	18 (30)
Apgar score, first minute	7 (4-8)
Apgar score, fifth minute	9 (5-10)
Birth weight (g)	3000 (1710–4100)
Neonatal intensive care unit (n, %)	19 (31.6)
Refusal to take care of the neonate (n, %)	6 (10)
Breastfeeding (n, %)	48 (80)

Note: Data given as median (Range: minimum–maximum) or number (percentage of the study population).

Three pregnant women had concomitant mental disorders along with AD.

The subtypes of AD observed in our study groups are shown in Table 2. Generalized anxiety disorder (GAD) was the most common diagnosis in the study group. Nineteen participants had panic disorder (PD), while five had substance-induced anxiety disorder. Thirty-six (60%) of the pregnant women were receiving medical treatment, and seven (11.6%) were under close psychiatric monitoring due to suicidal intentions. In total 28 patients were receiving medications for the treatment of SD which included, selective serotonin reuptake inhibitors (SSRIs) (n=20), a combination of SSRIs and atypical antipsychotics (n=5), and serotonin-norepinephrine reuptake inhibitors (n=3).

The outcomes regarding the pregnancy and delivery are of the patients are summarized in Table 3. Twelve patients delivered before 37 weeks of gestation. Five were diagnosed with hypertensive disorders of pregnancy, and one participant with substance-induced anxiety disorder underwent an emergency delivery due to placental abruption. Fetal anomalies observed in the neonates in our study werecongenital cataracts (n=1), microcephaly (n=1), ileal atresia (n=1), and agenesis of the corpus callosum (n=1). The median gestational age of newborns was 38 (range: 31–40) weeks, and the median birth weight was 3000 (range: 1710–4100) grams. Among the neonates requiring NICU care, 13 were monitored for respi-

https://doi.org/10.5455/annalsmedres.2025.01.026

ratory distress, two for sepsis, and one died due to prematurity. Six newborns were given to social services by the family.

DISCUSSION

Maternal adaptation during pregnancy and the establishment of a suitable intrauterine environment are essential for both maternal and fetal health. It is well known that pregnancy affects the hypothalamic-pituitary-adrenal axis. Corticotropin-releasing hormone, produced in large amounts by the placenta, a dynamic organ facilitating fetomaternal exchanges, significantly increases during pregnancy. Maternal adrenocorticotropic hormone levels rise, leading to physiological hypercortisolemia [4]. In the fetus, adrenal glands become prominent by the seventh week of gestation, and cortisol production begins in the early weeks [5]. However, mechanisms functioning harmoniously in utero can lose their homeostatic balance due to exogenous factors such as chronic stress. Chronic stress disrupts the normal circadian ofplacental corticotropin-releasing hormone, potentially altering the timing of delivery [6].

Numerous studies have investigated prenatal and postnatal outcomes in mothers with chronic stress factors such as AD and their offspring. Although the results vary, maternal psychological distress is generally believed to have an adverse effect on the fetus. Prenatal stress has been associated with changes in the placental transcriptome and impaired gene expression in trophoblasts [7]. Poor trophoblast development, widely recognized in literature as linked to various pregnancy complications, may contribute to the adverse fetal effects of anxiety by inducing gene changes due to stress. Another study found that mothers with high anxiety levels showed hypermethylation of placental genes, which was linked to hypotonia in their infants [8].

Maternal anxiety and anxiety disorders lead to epigenetic differences that result in adverse postnatal neurodevelopmental outcomes. Additionally, chronic anxiety was shown to enhance various neurotransmitter stimulations, increase maternal procoagulant mediators, induce vasoconstriction, and disrupt fibrinolytic activity, ultimately tipping the coagulation balance toward a prothrombotic state [9]. Similarly, maternal stress elevates interleukin-6 and tumor necrosis factor-alpha, creating a hyperinflammatory environment [10]. Recent research has demonstrated that prenatal stress and anxiety are associated with altered postnatal microbiome diversity in the neonates, that correlates with abnormal neurodevelopmental outcomes [11].

In a study comparing maternal psychometric scores with amniotic glucocorticoid and brain-derived neurotrophic factor (BDNF) levels, high glucocorticoid levels and elevated amniotic BDNF were associated with low birth weight and smaller head circumference. There was no correlation between psychometric scores and BDNF levels [12]. In a similar study on the same subject, childhood trauma scores in mothers were found to be associated with higher amniotic BDNF levels during pregnancy, but this was independent of glucocorticoid levels [13]. The increased presence of this mediator in the amniotic fluid during maternal anxiety is notableand it has a critical role in neuronal development and differentiation.

A national cohort study in the UK involving over two million participants found poor mental health to be associated with neonatal mortality and low birth weight [14]. Similarly, a national study in Hungary reported higher preterm birth rates among mothers with PD; however, no significant differences in average birth weights were noted compared to the general population [15]. Interestingly, anemia and polyhydramnios were more common among mothers with PD. A comprehensive study examining pregnancy outcomes with GAD, PD, and medication use found no significant association between GAD or PD and adverse outcomes. However, preterm birth and preeclampsia were more frequent among mothers using SSRIs, while low birth weight and increased cesarean delivery rates were linked to benzodiazepine use [16]. A retrospective cohort study in Australia involving over 50,000 pregnancies observed higher risks of preterm birth, low birth weight, and stillbirth in women hospitalized for psychiatric reasons within five years before pregnancy [17]. Community studies focusing solely on panic disorder have yielded similar findings [18,19]. In the current study, while the median birth weight of neonates from mothers with AD was within normal limits, preterm labor and hypertensive disorders of pregnancy were the most frequently observed complications.

A study conducted in Turkey reported NICU admission rates of 9.1% for treated PD cases and 25% for untreated cases [20]. In the current study, the number of newborns requiring NICU admission was 19. Excluding six infants given to social services and four admitted due to anomalies, the NICU rate dropped to 16.6%. Four infants born with structural anomalies had mothers who received medical treatment during the prenatal period. Meta-analyses have demonstrated a relationship between SSRI and antidepressant use, particularly during the first trimester, and an increased risk of fetal anomalies [21-23]. However, given the limited sample size of our study, these anomalies may be incidental. It is also noteworthy that we did not classify participants based on pharmacological treatment. All pregnant women in our study group were closely monitored by specialists for pharmacological or psychotherapeutic interventions. The current study indicates that 10% of mothers diagnosed with anxiety placed their infants into social services. Existing literature shows that Howard LM. et al. found that 70% of women with psychotic disorders discharged from mother and baby units were released with their mothers without formal supervision. The remaining 30% of infants were taken under supervision [24]. The study by Salmon et al. [25] found that 18% of mothers admitted with a psychiatric diagnosis had their babies taken into care by social services. Future nationwide research on maternal mental health and neonatal care is likely to offer more

https://doi.org/10.5455/annalsmedres.2025.01.026

definitive insights into this matter. Despite preterm birth being the most frequent complication, as reported in other studies, the median birth weight and gestational age in our study were within normal ranges. This outcome may reflect the benefits of multidisciplinary follow-up and efforts by healthcare professionals to manage maternal anxiety effectively with or without medication. Despite these findings, it is essential to note that some publications report no effect of anxiety diagnosed before pregnancy or mental health conditions on neonatal outcomes [26,27]. Proper monitoring of anxiety disorders is essential to protect mothers and their babies from adverse pregnancy outcomes and future developmental issues. More research is needed to understand the effects of anxiety and panic disorders on maternal and fetal health.

Limitations

Our study has several limitations. These include the lack of postnatal follow-up for the developmental outcomes of infants born from the patients in our study, and the absence of subgroup classification for AD. Furthermore, we did not establish a control group from gravid individuals who did not have AD.

CONCLUSION

Anxiety disorders are associated with adverse obstetric outcomes, particularly preterm birth.

Acknowledgments: The authors would like to thank healthcare professionals for their efforts to manage psychiatric disorders and protect maternal and infant health.

Ethics Committee Approval: This retrospective study was approved by the Ethics Committee of the Ankara City Hospital (TABED 2-24-644).

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author (BAA) upon request.

Informed Consent: The requirement for signed informed consent was waived as the data were anonymized and collected retrospectively from existing medical records.

Peer-review: Externally peer-reviewed.

Author Contributions: Design: B.A.A, D.Ş.; Data Collection and/or Processing: B.A.A.; Analysis and/or Interpretation: D.Ş.; Literature Review: B.A.A.; Writing: B.A.A.; Critical Review: D.Ş.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: This study did not receive any financial support.

REFERENCES

1. World Health Organisation https://www.who.int/news-room/fact-sheets/detail/anxiety-disorders. Access date September 27, 2023.
2. Republic of Turkey Ministry of Health, Health Statistics Annual Report https://dosyamerkez.saglik.gov.tr/Eklenti/40564/0/saglik-istatistikleri-yilligi-2019pdf.Access date June 09, 2021.
3. Hoirisch-Clapauch S, Brenner B, Nardi AE. Adverse obstetric and neonatal outcomes in women with mental disorders. *Thromb Res.* 2015;135 Suppl 1:S60-3. doi: 10.1016/S0049-3848(15)50446-5.
4. Mastorakos G, Ilias I. Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. *Ann N Y Acad Sci.* 2003;997:136-49. doi: 10.1196/annals.1290.016.
5. Johnston ZC, Bellingham M, Filis P, Soffientini U, Hough D, Bhattacharya S, et al. The human fetal adrenal produces cortisol but no detectable aldosterone throughout the second trimester. *BMC Med.* 2018;16(1):23. doi: 10.1186/s12916-018-1009-7.
6. Wadhwa PD, Culhane JF, Rauh V, Barve SS. Stress and Preterm Birth: Neuroendocrine, Immune/Inflammatory, and Vascular Mechanisms. *Matern Child Health J.* 2001;5(2):119-25. doi: 10.1023/a:1011353216619.
7. Nomura Y, Rompala G, Pritchett L, Aushev V, Chen J, Hurd YL. Natural disaster stress during pregnancy is linked to reprogramming of the placenta transcriptome in relation to anxiety and stress hormones in young offspring. *Mol Psychiatry.* 2021;26(11):6520-30. doi: 10.1038/s41380-021-01123-z.
8. Conradt E, Lester BM, Appleton AA, Armstrong DA, Marsit CJ. The roles of DNA methylation of NR3C1 and 11β-HSD2 and exposure to maternal mood disorder in utero on newborn neurobehavior. *Epigenetics.* 2013;8(12):1321-9. doi: 10.4161/epi.26634.
9. Hoirisch-Clapauch S, Nardi AE, Gris JC, Brenner B. Coagulation and mental disorders. *Rambam Maimonides Med J*. 2014;5(4):e0036. doi: 10.5041/RMMJ.10170.
10. Traylor CS, Johnson JD, Kimmel MC, Manuck TA. Effects of psychological stress on adverse pregnancy outcomes and nonpharmacologic approaches for reduction: an expert review. *Am J Obstet Gynecol MFM* . 2020;2(4):100229. doi: 10.1016/j.ajogmf.2020.100229.
11. Galley JD, Mashburn-Warren L, Blalock LC, Lauber CL, Carroll JE, Ross KM, et al. Maternal anxiety, depression and stress affects offspring gut microbiome diversity and bifidobacterial abundances. *Brain Behav Immun.* 2023;107:253-64. doi: 10.1016/j.bbi.2022.10.005.
12. Lamadé EK, Pedraz-Petrozzi B, Lindner O, Meininger P, Pisters A, Gilles M, et al. Stress in pregnancy - Implications for fetal BDNF in amniotic fluid at birth. *Neurobiol Stress.* 2024;31:100658. doi: 10.1016/j.ynstr.2024.100658.
13. Deuschle M, Hendlmeier F, Witt S, Rietschel M, Gilles M, Sánchez-Guijo A, et al. Cortisol, cortisone, and BDNF in amniotic fluid in the second trimester of pregnancy: Effect of early life and current maternal stress and socioeconomic status. *Dev Psychopathol.* 2018;30(3):971-80. doi: 10.1017/S0954579418000147.
14. Harron K, Gilbert R, Fagg J, Guttmann A, van der Meulen J. Associations between pre-pregnancy psychosocial risk factors and infant outcomes: a population-based cohort study in England. *Lancet Public Health.* 2021;6(2):e97-e105. doi: 10.1016/S2468-2667(20)30210-3.
15. Bánhidy F, Acs N, Puhó E, Czeizel AE. Association between maternal panic disorders and pregnancy complications and delivery outcomes. *Eur J Obstet Gynecol Reprod Biol.* 2006;124(1):47-52. doi: 10.1016/j.ejogrb.2005.04.013.
16. Yonkers KA, Gilstad-Hayden K, Forray A, Lipkind HS. Association of Panic Disorder, Generalized Anxiety Disorder, and Benzodiazepine Treatment During Pregnancy With Risk of Adverse Birth Outcomes. *JAMA psychiatry.* 2017;74(11):1145-52. doi: 10.1001/jamapsychiatry.2017.2733.
17. Dadi AF, He V, Brown K, Hazell-Raine K, Reilly N, Giallo R, et al. Association between maternal mental health-related hospitalisation in the 5 years prior to or during pregnancy and adverse birth outcomes: a population-based retrospective cohort data linkage study in the Northern Territory of Australia. *Lancet Reg Health West Pac.* 2024;46:101063. doi: 10.1016/j.lanwpc.2024.101063.

https://doi.org/10.5455/annalsmedres.2025.01.026

18. Chen YH, Lin HC, Lee HC. Pregnancy outcomes among women with panic disorder - do panic attacks during pregnancy matter? *J Affect Disord* 2010;120(1-3):258-62. doi: 10.1016/j.jad.2009.04.025.
19. Al-Awabdeh E, Abu Shaikha L, Salameh A, Alshraideh JA. Panic disorder during pregnancy: A scoping review. *Heliyon.* 2024;10(7):e28999. doi: 10.1016/j.heliyon.2024.e28999.
20. Uguz F, Yuksel G, Onur OS, Karsidag C, Gezginc K, Arpaci N. Neonatal outcomes in pregnant women with untreated and treated panic disorder. *Compr Psychiatry.* 2018;87:107-11. doi: 10.1016/j.comppsych.2018.10.001.
21. Bérard A, Zhao JP, Sheehy O. Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: an updated analysis of the Quebec Pregnancy Cohort. *BMJ Open.* 2017;7(1):e013372. doi: 10.1136/bmjopen-2016-013372.
22. Jimenez-Solem E, Andersen JT, Petersen M, Broedbaek K, Jensen JK, Afzal S, et al. Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study. *BMJ Open.* 2012;2(3). doi: 10.1136/bmjopen-2012-001148.
23. Gao SY, Wu QJ, Sun C, Zhang TN, Shen ZQ, Liu CX, et al. Selective serotonin reuptake inhibitor use during early pregnancy and congenital malformations: a systematic review and meta-analysis of cohort studies of more than 9 million births. *BMC Med.* 2018;16(1):205. doi: 10.1186/s12916-018-1193-5.
24. Howard LM, Thornicroft G, Salmon M, Appleby L. Predictors of parenting outcome in women with psychotic disorders discharged from mother and baby units. *Acta Psychiatr Scand.* 2004;110(5):347-55. doi: 10.1111/j.1600-0447.2004.00375.x.
25. Salmon MP, Abel K, Webb R, Warburton AL, Appleby L. A national audit of joint mother and baby admissions to UK psychiatric hospitals: an overview of findings. *Arch Womens Ment Health.* 2004;7(1):65-70. doi: 10.1007/s00737-003-0042-4.
26. Dwivedi AK, Sandhu N, Datta S, Gumber A, Shukla L, Yadav UK, et al. Association of antenatal anxiety with adverse pregnancy outcomes: A prospective hospital-based study. *Indian J Psychiatry.* 2023;65(3):368-72. doi: 10.4103/indianjpsychiatry.indianjpsychiatry_367_21.
27. Li H, Bowen A, Bowen R, Muhajarine N, Balbuena L. Mood instability, depression, and anxiety in pregnancy and adverse neonatal outcomes. *BMC Pregnancy Childbirth.* 2021;21(1):583. doi: 10.1186/s12884-021-04021-y.

https://doi.org/10.5455/annalsmedres.2025.01.026

Ann Med Res

Current issue list available at Ann Med Res

Annals of Medical Research

journal page: annalsmedres.org

Cytological and histopathological correlations of the Bethesda 3 categories in thyroid cytopathology: A 4-year single-center experience

Rabia Demirtas [a,*], Harika Derya Tamer [a]

[a]*Ataturk University, Faculty of Medicine, Department of Medical Pathology, Erzurum, Türkiye*
**Corresponding author: rabiademirtas@msn.com (Rabia Demirtas)*

MAIN POINTS

- The malignancy rate of repeat cytologies was similar to those directly operated after the first FNA(86.17% vs 77.2%). This suggests that the contribution of the second FNA to clinical decision making is limited.
- The postoperative malignancy rate was 83.45%, of which 36.8% were papillary microcarcinomas, most of which(<5 mm) may have been incidentally detected in the resection material. This may lead to an overestimation of the ROM.
- Malignancy rates were higher in single nodular goiters(45.5%) and significantly lower in multinodular goiters(14.1%) and cases with concomitant thyroiditis(5%). This suggests that multinodularity and chronic lymphocytic thyroiditis are associated with low ROM(p=0.0033).

Cite this article as: Demirtas R, Tamer HD. Cytological and histopathological correlations of the Bethesda 3 categories in thyroid cytopathology: A 4-year single-center experience. *Ann Med Res*. 2025;32(5):192--198. doi: 10.5455/annalsmedres.2024.12.277.

ABSTRACT

Aim: This study aimed to investigate the correlation between thyroid fine needle aspiration biopsy (FNAB) and thyroidectomy materials diagnosed as atypia of undetermined significance (AUS) with histopathological diagnoses over the last four years at our hospital.

Materials and Methods: This retrospective study included 251 thyroid FNAB cases with an AUS diagnosis referred to our laboratory between January 1, 2020, and December 31, 2023, and 133 of these patients who subsequently underwent surgery at our hospital.

Results: A histopathological diagnosis was made in 133 cases. Ninety-four patients were diagnosed after the first AUS diagnosis, and 39 after at least one control aspiration. Of the 39 patients who underwent a second cytological control, 56.4%(n=22) were diagnosed again with AUS. Of the surgical patients, 36.8%(n=49) were diagnosed with papillary microcarcinoma, 33.83%(n=45) with papillary carcinomas, 9.02%(n=12) with adenomatous hyperplasia and nodular hyperplasia, 6.7%(n=9) with invasive encapsulated follicular variant of papillary thyroid carcinoma, 3.75%(n=5) with follicular carcinoma, 3%(n=4) with chronic lymphocytic thyroiditis, 2%(n=3) with follicular adenoma, 1.5%(n=2) with well differentiated thyroid tumor of uncertain malignant potential, and 0.75%(n=1) each with medullary carcinoma, oncocytic carcinoma, anaplastic carcinoma-not otherwise specified, and paraganglioma. Because the majority (91.83%) of the cases diagnosed with papillary microcarcinoma were $\leq$5 mm in size, and there were benign nodular structures in non-tumor areas, aspiration was performed from benign nodules, and postoperative papillary microcarcinoma was detected incidentally.

Conclusion: In our study, most of the patients diagnosed with AUS had a diagnostic operation by the clinician, and the patients who underwent repeat cytology were mostly persistently diagnosed with AUS. It was remarkable that the majority (36.8%) of the patients diagnosed with AUS from an FNAB were diagnosed with incidental papillary microcarcinoma after resection. Since papillary microcarcinoma tumors are smaller than 1 cm, these cells are not sufficiently included in the cytology material from an FNAB.

Keywords: Histopathology, FNAB, Atypia of uncertain significance, Thyroid

Received: Dec 25, 2024 **Accepted:** Apr 18, 2025 **Available Online:** May 26, 2025

INTRODUCTION

Thyroid function is crucial for maintaining growth, development, and metabolic homeostasis [1]. A range of diseases are commonly associated with the thyroid gland, such as goiter, hyperthyroidism, hypothyroidism, thyroiditis, and neoplasms [1]. Most neoplasms are considered benign; however, the rate of malignant tumors in solitary nodules is 10% [1]. Although thyroid cancers are relatively rare, they account for 90% of all endocrine tumors [1]. A fine needle aspiration biopsy (FNAB) is an efficient and low-cost diagnostic technique that can be applied to palpable or non-palpable thyroid nodules suspected by radiologists [2,3]. FNAB is performed under ultrasound guidance in non-palpable lesions [2,3]. FNAB's sensitivity and specificity are 55%–98% and 73%–100%, respectively; however, it has limitations including diagnostic problems in inadequate samples, demanding sampling technique, and an overlap of benign and malignant cytologic features [1]. Two systems are used worldwide for the cytologic clas-

sification of thyroid lesions: the British Thyroid Association and the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) [2]. The TBSRTC classifies thyroid cytology specimens into six categories for more efficient reporting (Table 1) [2,4]. Not only the numerical classification but also the name of the category and numerical notation should be reported to avoid confusion; for example, "Atypia of uncertain significance (AUS) (Bethesda 3)" [4]. This has become the accepted mode of communication among the various specialties that deal with thyroid nodule diseases [5].

The AUS category defined by the TRBSRTC is used for cases without sufficient atypia for follicular neoplasia or malignant tumor and for which a definite diagnosis of benign or malignant is not made [4]. The term "follicular lesion of uncertain significance" (FLUS) was included in the "AUS" group to avoid confusion in the TBSRTC of 2023 [4].

Each category has a cancer risk, and the widespread adoption of the TBSRTC provides an approach to determine the risk of malignity (ROM) probability for each category [4]. As a result of a large-scale survey conducted in 2017, information on the ROM for each category was updated [4], as presented in Table 1.

The number of patients with cancer after subsequent surgery was considered when calculating the ROM [1]. However, the ROM is overestimated because the number of nodules resected glands in nondiagnostic, benign, or AUS-diagnosed cytologies is lower [4,5].

The effect of "Non-invasive follicular variant papillary thyroid carcinoma" (NIFTP) on ROM is another issue [4]. NIFTP is a surgical diagnosis that cannot be known for sure using an FNAB [4]. The examination of NIFTP cytological features indicates that these nodules tend to be classified as AUS (Bethesda 3), follicular neoplasia (Bethesda 4), or suspected malignancy (Bethesda 5) from an FNAB, which affects the ROM results [4].

Compared with the histopathologic resection results of patients diagnosed with AUS, the ROM was 22% (range 20-32%) (Table 1) [4]. ROM is also affected by whether the diagnosis of AUS is based on nuclear or structural atypia [4,6]. According to the most recently reported data, the ROM in AUS cases diagnosed based on nuclear atypia was 59%, while it was 6.5% in those diagnosed based on structural or oncocytic atypia, which is close to the ROM rate of cases with benign cytology (1–3%) [4,6]. TBSRTC 2023 classified AUS into two subcategories, "nuclear" and "other," and emphasized the importance of cases diagnosed with nuclear atypia-based AUS to improve patient management for clinicians and cytopathologists [4]. In cases diagnosed with AUS, the absence of nuclear atypia should be considered to avoid unnecessary surgery [6]. The incidence of malignancy is similar between patients diagnosed with AUS from initial cytology and those diagnosed with malignancy after consecutive cytology; therefore, consecutive FNABs may not have a clear benefit in terms of clinical decision-making [5]. The present study aimed to examine thyroid FNABs diagnosed with AUS in the last 4 years at the hospital where the study was conducted and to determine the correlation of these cases with postoperative histopathologic diagnoses.

MATERIALS AND METHODS

A retrospective study was conducted between 01.01.2020 and 31.12.2023, and cases with histopathological diagnosis data among those diagnosed with AUS using an FNAB in our laboratory were included in the study. Cases with histopathologic right/left lobectomy or total thyroidectomy were included. Core biopsies, recurrent malignancies, and completion thyroidectomy were excluded.

FNAB was performed by head and neck specialists, endocrinologists, and radiologists using ultrasound guidance or palpation with a 25-or 27-gauge needle. Nodules diagnosed as AUS for the first time underwent repeat FNAB or resection, depending on the consent of the patient and the clinician following the patient. Patients who were diagnosed with AUS repeatedly were resected for diagnosis and treatment, again with the consent of the patient. Increased nodule size, large multinodular appearance, clinical suspicion, and patient preference were among the operative criteria.

The evaluations were performed by two pathologists. The diagnosis of AUS was evaluated according to the criteria defined in the TRBSRTC guidelines, taking into evaluation nuclear atypia (nuclear enlargement and contour irregularity), architectural atypia (prominent microfollicles and oncocytic atypia (presence of predominant oncocytic features) [7]. Cases diagnosed with FLUS were reclassified according to the 2023 Bethesda system [4].

Pathology reports of each case were obtained digitally from the hospital's information record system. Approval was obtained from the authorized units for files analysis in the digital environment.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, Version 26.0 (Armonk, NY). Power analysis was conducted using F-tests and by calculating effect sizes to determine if the statistical tests had sufficient power. The normality of continuous variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Continuous measurements were summarized as mean and standard deviation. Categorical variables were analyzed using Chi-square tests (including Fisher-Freeman-Halton where appropriate), Kruskal-Wallis, and ANOVA tests. The statistical significance level was set at 0.05 for all tests.

Within this context, 251 FNAB cases with an initial diagnosis of AUS and 133 patients who underwent surgery were included in the study. The rate of control cytology samples was analyzed in cases with an initial AUS diagnosis. Fi-

https://doi.org/10.5455/annalsmedres.2024.12.277

nally, the correlation between the cytologic and corresponding histopathologic diagnoses was evaluated.

RESULTS

There were 251 patients diagnosed with AUS in our department, and 133 of these cases had resection material available in our unit. Of these cases, 73% (n=97) were female, 27% (n=36) were male, and the female-to-male ratio was 2.69:1. These cases were aged between 17 and 79 years, with a mean age of 48.6 ± 12,3 years. According to the results of the analysis, the mean age of the malignant group was 48.92 ± 12.46 years, that of the benign group was 49.15 ± 10.50 years, and that of the group with uncertain malignancy potential was 33.00 ± 21.21 years (p = 0.193). The age range with the highest number of cases was 41–50 (30.7%), followed by 54–60 (24.06%). The patient sex and age distributions are shown in Figure 1.

Power analysis using the F-test revealed a statistical power of 99.99%, confirming that the analyses were adequately powered to detect statistically significant differences, should they be present.

Following an initial diagnosis of AUS, a histopathologic diagnosis was reached in 70.6% of cases (n=94), while an additional 29.3% (n=39) received a histopathologic diagnosis after at least one control aspiration. Among the resected thyroid tissues with a single AUS diagnosis, 86.17% (n=81) were malignant, 12.7% (n=12) were benign, and 1.06% (n=1) were lesions of uncertain malignant potential (Figure 2). Of the 39 patients undergoing a second cytology control that had resection material, 10.2% (n=4) were diagnosed with non-diagnostic cytology, 15.3% (n=6) with benign cytology, 56.4% (n=22) with recurrent AUS, 2.5% (n=1) with follicular neoplasia, 12.8% (n=5) with suspected malignancy, and 2.5% (n=1) with malignant cytology. Compared with using the resection material, 76.9% (n=30) of the patients undergoing a second cytology were malignant, 20.5% (n=8) benign, and 2.5% (n=1) neoplasia of uncertain malignancy potential (Figure 3). The resection of 22 cases diagnosed with AUS after the second cytology resulted in 77.2% (n=17) malignant and 22.8% (n=5) benign thyroid lesions.

Among the 133 patients who underwent surgery, 83.45% (n=111) were histopathologically reported as malignant, 15.03% (n=20) as benign thyroid lesions, and 1.5% (n=2) as uncertain malignant potential. The individual analysis of the diagnoses revealed that 36.8% (n=49) of the patients had papillary microcarcinoma, 33.83% (n=45) papillary carcinoma, 9.02% (n=12) follicular nodular disease, 6.7% (n=9) invasive encapsulated follicular variant papillary thyroid carcinoma (IEFV-PTC), 3.75% (n=5) follicular carcinoma, 3% (n=4) chronic lymphocytic thyroiditis(CLT), 2.2% (n=3) follicular adenoma, and 1.5% (n=2) well-differentiated thyroid carcinoma of uncertain malignant potential (WDT-UMP). In addition, 0.75% (n=1) of the patients was diagnosed with medullary carcinoma, oncocytic carcinoma, anaplastic carcinoma-NOS, and paraganglioma.

Table 1. 2023 Bethesda system for reporting thyroid cytopathology.

Diagnostic category		ROM** mean % (range)
Category 1	Non-diagnostic	13 (5–20)
Category 2	Benign	4 (2–7)
Category 3	AUS*	22 (13–30)
Category 4	Follicular neoplasia	30 (23–34)
Category 5	Suspicion of malignancy	74 (67–83)
Category 6	Malignant	97 (97–100)

**AUS: Atypia of Undetermined Significance **ROM: Risk of malignancy.*

The analyses of the cases diagnosed with papillary microcarcinoma indicated that 45 of 49 were 5 mm or less in size, and structures such as follicular nodular disease of the thyroid (n=25), chronic lymphocytic thyroiditis (n=16), follicular adenoma (n=5), oncocytic adenoma (n=1), and neoplasia of uncertain malignancy potential (n=2) were observed in non-microcarcinoma areas. Most of the cases (91.83%) diagnosed with papillary microcarcinoma were ≤5 mm in size, and there were lesions observed in non-tumor areas; therefore, it was concluded that aspiration was performed from other accompanying nodules and that papillary microcarcinoma was detected incidentally postoperatively. When the incidental papillary microcarcinoma diagnoses were excluded, a malignant tumor rate of 49.62% was obtained. The histopathologic classifications of the nodules resulting in the diagnosis of AUS are presented in Table 2.

Twenty-two cases had nodular formation, 71 cases had multinodular formation, 20 cases had chronic lymphocytic thyroiditis, and 20 cases had no additional features in non-tumor areas. In order to evaluate the malignancy rates according to the criteria of nodular goiter (group 1), multinodular goiter (group 2), CLT and no feature in non-tumor areas, and CLT and no feature (group 3) were included in a single group, and statistical analysis revealed a significant difference (p=0.0033). In the first group, the malignant tumor rate was 45.5%. In the second and third groups, this rate gradually decreased. The malignant tumor rates were 14.1% and 5% in the second and third groups, respectively. When malignancy rates were analyzed, it was seen that malignant tumor rates were significantly higher in nodular goiter patients compared to other groups. There was a significant decrease in malignant tumor rates with an increase in the presence of multinodular formation, chronic lymphocytic thyroiditis, and cases with no features.

When the median, minimum and maximum values were calculated in the statistical Kruskal-Wallis test (p = 0.559) in terms of TSH hormone level according to malignancy status, the median TSH hormone values in the malignant group were 1. 491 mU/L (0.005 - 103.72) in the malignant group, 1.789 mU/L (0.398 - 8.470) in the benign group and 2.318 mU/L (1.817 - 2.819) in the group with uncertain malignancy potential. The mean T4 hormone levels calculated using one-way ANOVA test was 0.977 ± 0.284 ng/dL in the malignant

https://doi.org/10.5455/annalsmedres.2024.12.277

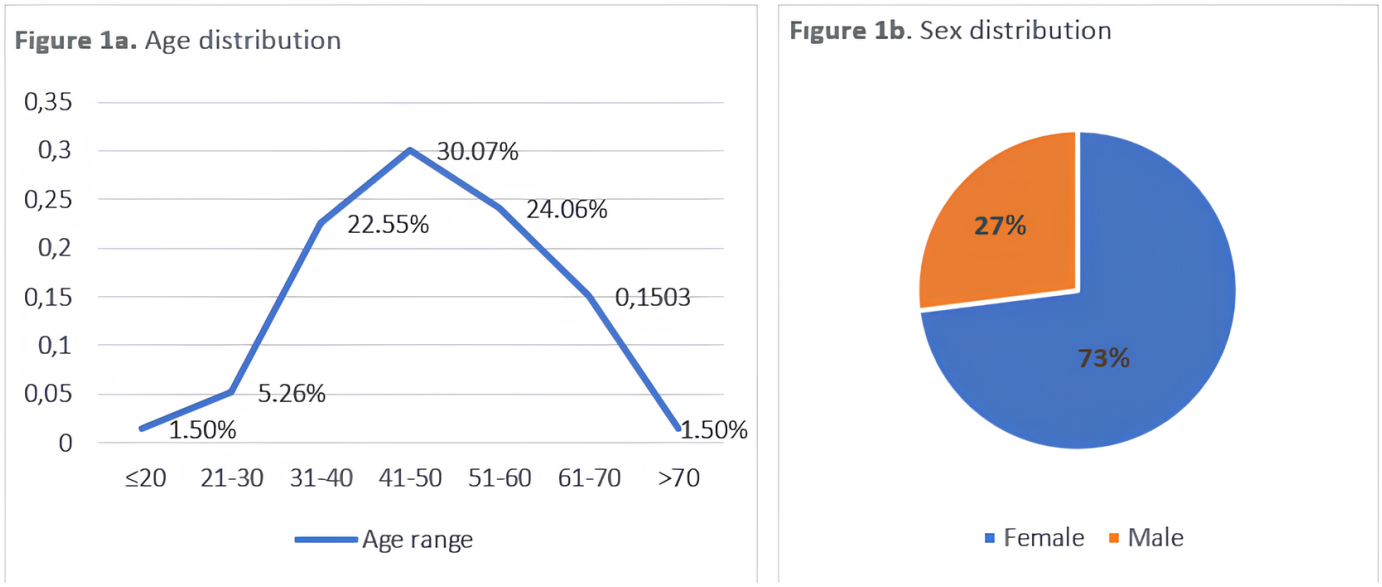

Figure 1. a,b. The distribution of the age (a) and sex of the study population (b).

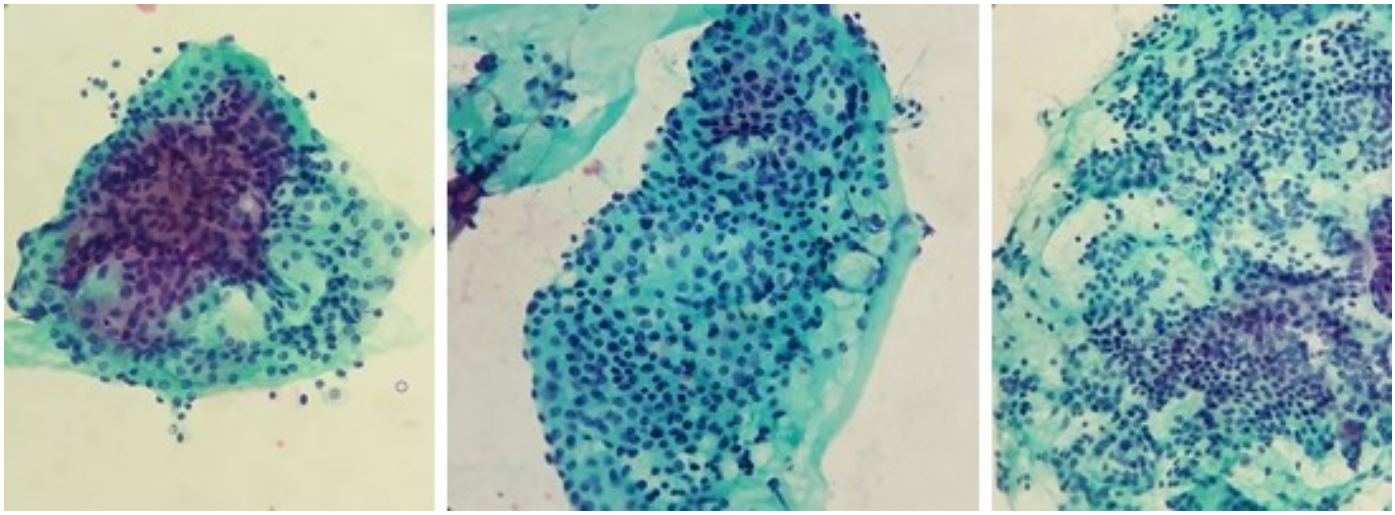

Figure 2. Bethesda 3 category in cytology; 40x, pap.

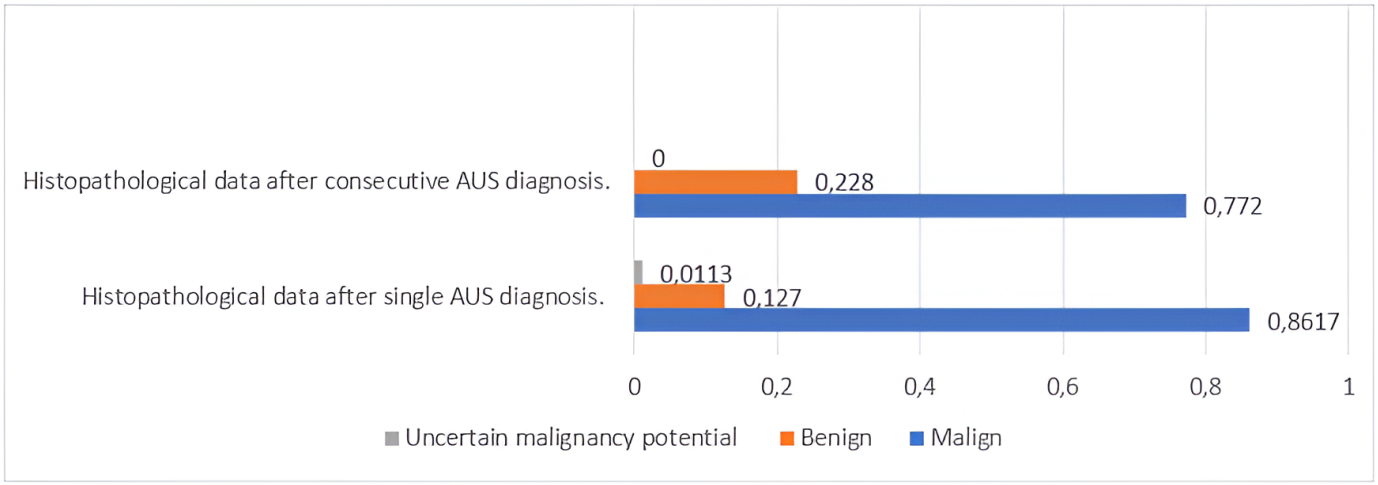

Figure 3. Comparison of the histopathologic results of patients diagnosed with AUS after a single diagnosis of Atypia of Undetermined Significance and cases diagnosed with AUS after repeated fine needle aspiration biopsy.

https://doi.org/10.5455/annalsmedres.2024.12.277

Table 2. Histopathologic distribution of cases diagnosed with atypia of undetermined significance.

Histopathologic diagnosis	Papillary carcinoma*	Papillary microcarcinoma	Follicular carcinoma	Medullary carcinoma	Anaplastic carcinoma	Oncocytic carcinoma	Other **	Benign ***
Number of cases	54	49	5	1	1	1	3	19
Distribution (%)	40.6%	36.8%	3.8%	0.75%	0.75%	0.75%	2.25%	14.3%

IEFV-PTC: included in papillary carcinoma ** WDT-UMP and paraganglioma were included in this group * Follicular nodular disease of the thyroid, chronic lymphocytic thyroiditis, and follicular adenoma were included in this group*

group, 0.960 ± 0.207 ng/dL in the benign group and 0.920 ± 0.113 ng/dL in the group with uncertain malignancy potential (p = 0.927). According to these results, there was no statistically significant difference between the malignant, benign, and certain malignant tumor potential groups in terms of TSH hormone(p=0.887) and T4 hormone levels (p=0.927).

DISCUSSION

Thyroid nodules are detected in 4–8% of adults using physical examination, 41% using radiological methods, and 50% during autopsy [8]. The American Thyroid Association and the National Comprehensive Cancer Network recommend the use of FNAB as the first diagnostic test because of its diagnostic reliability and cost-effectiveness [8]. FNAB avoids unnecessary surgery for benign nodules [8]. Cytopathologic data obtained after FNAB are classified into six categories based on the Bethesda system: non-diagnostic, benign, AUS, follicular neoplasm, suspicion of malignancy, and malignant [4]. Our department included cases diagnosed with FLUS classified according to the pre-2023 Bethesda system, and these cases were reclassified and evaluated according to the current Bethesda classification.

The ages of the patients in this study ranged from 17 to 79 years, and the mean age was 48.6 years. Of these patients, 73% (n=97) were female and 27% (n=36) were male, with a female-to-male ratio of 2.69:1. The incidence of thyroid lesions was higher in women than in men, a rate similar to the incidence of higher thyroid lesion rates in women (77.34%) in the study conducted by Machata et al. examining all Bethesda categories [9]. In addition, the age distribution of lesions in the study by Machata et al was most frequently between 41 and 50 (25–59%), followed by those between 51 and 60 (22.35%). In the present study, the age distribution was most frequent in the fifth decade, followed by the sixth decade, which was a similar range [9]. Furthermore, Machata et al. found that the post-resection malignancy rate of cases in the Bethesda 3 category was 17.1% [9].

The study conducted by Ho et al. included 350 patients diagnosed with AUS who had immediate surgery, and the ROM was 38.6%, whereas 31 patients underwent repeated FNAB, and the ROM was 37.8% [5]. The majority of cases resulting in malignant cytology were diagnosed as papillary thyroid carcinoma [5]. The cases with benign surgical results were diagnosed with nodular hyperplasia [5]. The rate of cases with benign lesions in the resection material was 14.3% (n=19) in the present study. Follicular nodular disease of the thyroid, chronic lymphocytic thyroiditis, and follicular adenoma were among them. Ho et al. also found incidental thyroid cancer in 85 patients, of whom 76 (89.4%) had a diagnosis of papillary microcarcinoma and the ROM rate was 57.2% with the inclusion of incidental cases. In the present study, papillary carcinoma and papillary microcarcinoma were the most common malignancies, followed by follicular carcinoma. Moreover, the ROM in the present study was 49.62%; with the inclusion of incidental carcinoma cases (papillary microcarcinoma), the ROM was 83.4%, which was higher than that in the literature. This shows that incidental malignant lesions increase the ROM rate in cases diagnosed with AUS and reveals that this risk ratio is not clear in cases diagnosed with AUS.

VanderLaan et al. conducted a study with 331 cases and found that the malignancy rate was 41% in cases diagnosed with AUS after the first FNAB who underwent immediate surgery and 43% in those cases after a repeated FNAB. They determined the rthat the of malignant tumor after a single AUS or recurrent AUS diagnosis was similar and higher than 40% [10]. However, in the present study, the postoperative malignant tumor risk of cases with a first diagnosis of AUS was 86.17% and that of cases with consecutive FNABs was 77.2%, which were close rates. These data suggest that consecutive FNABs do not provide a clear benefit in terms of clinical resection decisions. In addition, VanderLaan et al reported the malignant tumor rate of 45.7% in all surgical cases, a rate higher than that reported in the literature [10]. In the present study, the malignant tumor risk obtained by excluding incidental papillary microcarcinomas was 49.62%, which was similar to that of that study. In the study conducted by VanderLaan et al., 89% (n=81) of the cases diagnosed with malignancy were papillary carcinoma, followed by follicular carcinoma at a rate of 9% (n=8) [10]. The most common malignant tumor was papillary carcinoma in the present study.

Başçeken et al evaluated the correlation between the diagnosis of AUS and the histopathological correlation and found the rate of malignant tumor was higher than the literature, with a rate of 43.5% [11]. In addition, another study conducted in Turkey found that ROM was 49.1% in AUS cases [12]. These results are similar to the ROM rates calculated in the present study by excluding incidental cases.

In another study, although the risk of malignant tumor was approximately 35% in cases diagnosed with AUS, it was 51.9% in those with a second diagnosis of AUS. The study also re-

https://doi.org/10.5455/annalsmedres.2024.12.277

ported that the ROM decreased to 5.3% if radiologic data did not suggest malignant tumor when the results were evaluated together with ultrasonographic data. In addition, the same study emphasized that clinicopathological and ultrasound results should also be considered when evaluating the malignant tumor rate in cases diagnosed with AUS [13].

In an analytical review of 47 studies including 4,475 cases of AUS, Huhtamella et al reported the malignant tumor risk rate of 27% (23–31%). Histopathologically confirmed ROM after the first FNAB was 38.2%; however, the ROM after the second FNAB was 21.7%. The study also found a significant correlation between nuclear atypia, which we mentioned earlier, and a higher ROM rate in cytology materials diagnosed with AUS [14]. In addition, the authors reported ROM of 16.7% with focal features suggestive of papillary carcinoma, 12.2% with cytologic atypia, and 12% with architectural atypia [14]. These data show that cases with nuclear atypia have a higher ROM rate and partially explain these variations in ROM rates [14].

Of the 33 cases diagnosed with papillary microcarcinoma, 31% (n=10) had a cytologic diagnosis of AUS in the study conducted by Şeker et al. The study also emphasized that false-negative results were obtained, especially in nodules smaller than 5 mm, because of inadequate sampling [15]. In another similar study, the resection result of papillary microcarcinoma in cases with a false-negative diagnosis may have resulted from the lack of optimal sampling of these areas or the presence of other accompanying nodules and also attributed the reason for resection in these cases to the result of evaluation with detailed clinical, radiological, and pathological data [16]. In the present study, 49 of the resected thyroidectomy materials had a diagnosis of papillary microcarcinoma, and in 45 of these cases, the carcinoma size was 5 mm or smaller. In addition, benign lesions, such as follicular nodular disease and chronic lymphocytic thyroiditis, were observed in the investigation of thyroid tissue outside these carcinoma areas.

Some studies have excluded papillary microcarcinomas [3] or have not included them in the ROM because they are detected incidentally [5]. Some patients are not detected by clinical examination or are diagnosed incidentally. In the present study, it is thought that these tumors, which are incidental and smaller than 1 cm in size, may not contribute cells to the slides from an FNAB and should not be included because they increase the ROM rate after resection. Accordingly, more research is needed on this subject. In addition, clinical, radiological, and pathological data should be considered by clinicians in cases diagnosed with AUS because many factors affect ROM.

CONCLUSION

This study determined that the patients diagnosed with AUS in our unit were mostly taken to surgery directly, and in cases with repeated FNABs, the cytopathologic result was mostly AUS. In addition, the malignant tumor rates were similar in AUS cases that directly underwent surgery or surgery after consecutive FNABs. In this study, most cases diagnosed as AUS (84.9%) were malignant.

However, some papillary microcarcinomas are not detected during clinical examination but are detected during the pathologic examination of thyroid specimens after surgery. Compared with the resection specimens in our unit, it is noteworthy that papillary microcarcinoma (n=45), which was detected in the resection specimens of patients diagnosed with AUS, constituted a large proportion of the diagnoses (33.83%). This suggests that because papillary microcarcinomas are tumors smaller than 1 cm, these cells may not be included in the cytology material from an FNAB, and cytological sampling is performed from other accompanying nodules. The high ROM rate in the cases with AUS is attributed to papillary microcarcinoma features. The rate of ROM was 49.62%, excluding incidental cases of papillary microcarcinoma.

Tumoral cells may not be sampled on the slide from tumors smaller than 1 cm in size and may be incidentally detected in the resection material during FNAB. FNAB is a valuable method that deserves the importance given to it in the diagnosis and follow-up of thyroid nodules; however, the most appropriate decision should be reached by evaluating the patient's clinical, radiological, and laboratory results as a whole. In addition, there are many factors affecting ROM, and incidental malignancies should not be included in the calculation of ROM.

Ethics Committee Approval: Ethical approval was obtained from Atatürk University Non-Interventional Research Ethics Committee with a decision dated March 29, 2024, meeting number: 2 and, decision number: 19.

Informed Consent: Since the current study was a retrospective analysis, ethics committee approval was obtained and informed consent form was not necessary for this manuscript.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: RD, Design: HDT, Supervision, Material support: RD, Data collection and/or processing: HDT, Data analysis and interpretation: RD, Literature Review: HDT, Writing: HDT, Critical revision of manuscript: RD, HDT.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: The authors declare no financial support.

REFERENCES

1. Singh P, Gupta N, Dass A, Handa U, Singhal South Correlation of fine needle aspiration cytology with histopathology in patients undergoing thyroid surgery. *Otolaryngol Pol.* 2020;75(2):1-5. doi:10.5604/01.3001.0014.3433.
2. M. Syed, N. Akhtar, M. Hameed, et al. Cytological and histopathological correlation of thyroid lesions. *J Pak Med Assoc.* 2022;72(2):300-304. doi:10.47391/JPMA.2224.

https://doi.org/10.5455/annalsmedres.2024.12.277

3. Tessler I, Cohen O, Shochat I et al. Outcomes of the Bethesda system for reporting thyroid cytopathology in community- vs. institution-performed cytology. *Am J Otolaryngol.* 2022;43(2):103341. doi:10.1016/j.amjoto.2021.103341.
4. Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, VanderLaan PA. The 2023 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid.* 2023;33(9):1039-1044. doi:10.1089/thy.2023.0141.
5. Ho AS, Sarti EE, Jain KS, et al. Malignancy rate in thyroid nodules classified as Bethesda category III (AUS/FLUS). *Thyroid.* 2014;24(5):832-839. doi:10.1089/thy.2013.0317.
6. Cherella CE, Hollowell ML, Smith JR, et al. Subtype of atypia on cytology and risk of malignancy in pediatric thyroid nodules. *Cancer Cytopathol.* 2022;130(5):330-335. doi:10.1002/cncy.22544.
7. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid.* 2017;27(11):1341-1346. doi:10.1089/thy.2017.0500.
8. Sezen Koçarslan, Bayram Erol Altunbaş, Muhammet Emin Güldür, Fatıma Nurefşan Boyacı, Ahmet Şeker. (2013). Tiroid ince iğne aspirasyon biyopsilerinin histopatolojik sonuçlar ile retrospektif olarak değerlendirilmesi. *Harran Üniversitesi Tip Fakültesi Dergisi.* (Vol. 10, pp. 26–31). Vol. 10, pp. 26–31.
9. Machała E, Sopiński J, Iavorska I, Kołomecki K. Correlation of Fine Needle Aspiration Cytology of Thyroid Gland with Histopathological Results. *Pol Przegl Chir.* 2018;90(6):1-5. doi:10.5604/01.3001.0012.4712.
10. VanderLaan PA, Marqusee E, Krane JF 2011 Clinical outcome for atypia of undetermined significance in thyroid fine-needle aspirations: should repeated FNA be the preferred initial approach? *Am J Clin Pathol.* 135:770–775. doi: 10.1309/AJCP4P2GCCDNHFMY.
11. Başçeken Sİ, Tikici D. Önemi Belirsiz Atipili Hastalardaki Postoperatif Histopatolojik Malignite Varlığı. *Med J SDU.* 2023;30(1):119-22. doi: 10.17343/sdutfd.1236410.
12. Akın Ş, Helvacı N, Çınar N, Önder S, Bayraktar M. Atypia of Undetermined Significance in Thyroid Fine-Needle Aspiration Cytology: Pathological Evaluation and Risk Factors for Malignant tumor. *South Clin Ist Euras.* 2017; 28(2): 82-86. doi: 10.14744/scie.2017.54926.
13. Ryu YJ, Jung YS, Yoon HC, et al. Atypia of undetermined significance on thyroid fine needle aspiration: surgical outcome and risk factors for malignancy. *Ann Surg Treat Res.* 2014;86(3):109-114. doi:10.4174/astr.2014.86.3.109.
14. Huhtamella R, Kholová I. Thyroid Bethesda Category AUS/FLUS in Our Microscopes: Three-Year-Experience and Cyto-Histological Correlation. *Cancers (Basel).* 2019;11(11):1670. Published: 28 October 2019. doi:10.3390/cancers11111670.
15. Şeker NS, Kaya Ş, Şenol A, Soylu H. Tiroid Nodüllerinde Sitopatolojik Ve Histopatolojik Uyum Değerlendirmesi: 425 Olgu İçeren Tek Merkez Çalışması. *Kafkas Tip Bil Derg.* August 2021;11(2):282-287. doi: 10.5505/kjms.2021.46362.
16. İmamoğlu Ç, İmamoğlu FG, Dizen H, Argon A, Adıbelli ZH, Cengiz BP, Düzgöl C, Çalan M, Arslan E, Adatepe M, Kebat T. Tiroid Nodüllerinde Ultrasonografi Eşliğinde İnce İğne Aspirasyon Sitolojisi: Sitohistolojik Korelasyon. *Muğla Sıtkı Koçman Üniversitesi Tip Dergisi.* Aralık 2015;2(3):7-11.

https://doi.org/10.5455/annalsmedres.2024.12.277

Ann Med Res

Current issue list available at Ann Med Res

Annals of Medical Research

journal page: annalsmedres.org

A retrospective comparative study: Novel diagnostical markers of inflammation and cardiovascular risk of bipolar disorder and manic episode

Elif Ozcan Tozoglu

University of Health Sciences, Erzurum Faculty of Medicine, Department of Psychiatry, Erzurum, Türkiye

**Corresponding author: elif.ozcantozoglu@sbu.edu.tr (Elif Ozcan Tozoglu)*

MAIN POINTS

- Inflammatory (PIV, IBI) and atherogenic (AIP) indices were significantly elevated in manic and remission phases of bipolar disorder (BD), compared to healthy controls.
- PIV and IBI emerged as strong predictors of manic episodes and showed positive correlation with episode severity.
- AIP was significantly higher in the remission group, suggesting an underlying atherogenic tendency possibly linked to treatment and lifestyle.
- Easily accessible markers (PIV, IBI, AIP) may serve as novel, cost-effective biomarkers for BD monitoring and manic episode prediction.
- The study included drug-naive patients, enhancing the reliability of biomarker-disease associations.

Cite this article as: Ozcan Tozoglu E. A retrospective comparative study: Novel diagnostical markers of inflammation and cardiovascular risk of bipolar disorder and manic episode. *Ann Med Res*. 2025;32(5):199--209. doi: 10.5455/annalsmedres.2025.01.019.

ABSTRACT

Aim: The pan-immune inflammation value (PIV), inflammation burden index (IBI), atherogenic index of plasma (AIP), neutrophil/ high-density lipoprotein (HDL) ratio (NHR), lymphocyte/HDL ratio (LHR), monocyte/HDL ratio (MHR), and platelet/HDL ratio (PHR) have recently been investigated as novel inflammatory and cardiovascular markers. Our study aimed to compare these indices with the manic episode and remission period of bipolar disorder (BD) patients with controls and to investigate the relationship between these indices and the clinical characteristics of the patients and whether these indices can be biomarkers for the disease and manic episode.

Materials and Methods: In this retrospective observational study, we collected data from 66 patients in remission, 67 patients with manic episodes, and 70 controls. Differences in PIV, IBI, AIP, NHR, MHR, LHR, and PHR were investigated. We performed logistic regression analysis to identify predictors of manic episodes, and the diagnostic potential of these parameters was evaluated using ROC curves.

Results: Significant differences were found between the three groups in NHR (p<0.001), MHR (p=0.001), LHR (p=0.013), AIP (p<0.001), PIV (p<0.001) and IBI (p<0.001). IBI (p<0.001) and PIV (p:0.001) were found to be positive predictors of manic episodes. ROC analysis showed that IBI (p<0.001) and PIV (p<0.001) can be used to define a manic episode; IBI (p<0.001), PIV (p<0.001) and AIP (p:0.001) can be used to define BD.

Conclusion: Given the inflammatory and atherogenic processes involved in the etiopathogenesis, the novel biomarkers PIV, IBI, and AIP may be promising therapeutic targets for BD. In addition, these biomarkers can be used as easily accessible, inexpensive clinical tools to predict illness and severity of manic episodes.

Keywords: Pan-immune-inflammation value, Inflammatory burden index, Atherogenic index of plasma, Bipolar disorder, Biomarker

Received: Jan 17, 2025 **Accepted:** Apr 18, 2025 **Available Online:** May 26, 2025

INTRODUCTION

Bipolar Disorder (BD) is a recurrent and chronic illness characterized by mania, hypomania, depression, and mixed-type episodes leading to decreased quality of life, limitation, and mood fluctuations [1]. The worldwide prevalence of BD is reported to be between 2% and 5% [1]. In addition to the hypotheses that genetic factors, disruption in calcium signaling mechanisms, mitochondrial dysfunction, neuroplasticity, and neurotrophic factor disorders, oxidative stress, and neurotransmitter systems play a role in the etiology of BD, inflammatory reactions have recently been thought to play a role in pathogenesis. Therefore, it is suggested that it may be possible to consider BD as a multisystemic inflammatory disease [2]. The relationship between BD and inflammation has recently been the subject of many studies, and the number of publications on the effects of inflammation on disease progression and treatment efficacy is increasing. Studies have shown that the incidence of diseases such as immune-related hyperthy-

roidism, rheumatoid arthritis, and polymyalgia rheumatica is higher in patients with BD compared to the healthy population [3]. In addition, cardiovascular risks and activation of atherogenetic mechanisms are increased in patients with severe mental disorders due to both the lifestyle brought on by the disease and the long-term use of antipsychotics and mood stabilizers. The inflammation observed in BD may be a secondary physiological response that occurs during the course of the disease rather than the primary cause of the disease. However, since the markers used to prove and monitor these conditions are expensive and laborious, indices that can be obtained by routine examinations have recently been used to predict the prognosis of diseases with high inflammatory and cardiogenic risk and cancers.

Studies on inflammation have focused on neutrophil, lymphocyte, platelet, platelet, platelet count, and C-reactive protein (CRP) levels, whereas studies on cardiovascular risk have focused on lipid profiles. The neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios serve as convenient markers for assessing inflammation in BD because of their derivation from routine blood count tests. Research has identified notable disparities in these ratios when comparing patients with BD to healthy individuals [4]. C-reactive protein (CRP), a key acute-phase reactant, is produced in response to inflammatory triggers and is predominantly controlled by proinflammatory cytokines. Factors such as anemia, protein levels, red blood cell morphology, age, or sex do not affect CRP levels [5]. CRP is considered a reliable biomarker of inflammation and is frequently used to measure low-grade inflammation in both physical and mental health conditions. Research indicates that CRP levels are consistently higher in individuals with bipolar disorder (BD) than in healthy controls, regardless of episodic state, but they tend to rise significantly during manic episodes [6].

The Pan-immune inflammation value (PIV) and inflammatory burden index (IBI), which are based on these, are newly defined biomarkers that can potentially reflect the body's immune response and systemic inflammation status. PIV, initially introduced by Fuca et al., is calculated by dividing the combined product of neutrophil, platelet, and monocyte counts by the lymphocyte count [7]. This metric has been linked to disease prognosis in various inflammation-related conditions, including colorectal cancer, antineutrophil cytoplasmic antibody-associated vasculitis, and ST-segment elevation myocardial infarction [7-9].

The Inflammatory Burden Index (IBI) is an emerging marker used to evaluate systemic inflammation and immune function. The value is calculated by multiplying C-reactive protein (CRP) by the neutrophil-to-lymphocyte ratio (NLR). Initially introduced by Xie et al, IBI serves as a tool for measuring the inflammatory burden in various cancers and predicting patient prognosis [10]. A study involving patients with Alzheimer's disease, a condition in which inflammation is believed to play a role in its development, found that IBI levels were significantly higher in patients than in healthy controls [11].

Recent evidence highlights the crucial role of inflammation in the development of atherosclerosis. Research on chronic inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis has demonstrated the contribution of systemic inflammation to the progression of atherosclerosis. These conditions are also linked to an increased risk of cardiovascular disease and early-onset atherosclerosis [12]. Among the modifiable risk factors for atherosclerotic cardiovascular disease, the lipid profile is particularly significant [13]. Lipid profile assessments typically include total cholesterol (TC), high-density-lipoprotein (HDL), low-density-lipoprotein (LDL), and triglycerides (TG).

HDL plays a vital role in the lipid profile by preventing the buildup of free cholesterol and triglycerides (TG) in blood vessels. It shields endothelial cells from the harmful effects of LDL and inhibits LDL oxidation. Additionally, HDL offers numerous protective benefits, such as anti-inflammatory, antioxidant, antithrombotic, anti-infective, and immunomodulatory effects [14]. Studies suggest that HDL interacts with immune cells like neutrophils, lymphocytes, monocytes, and platelets, limiting neutrophil activation, adhesion, migration, and monocyte-driven processes [15].

Considering the roles of neutrophils, monocytes, lymphocytes, platelets, and HDL in inflammatory processes, several ratios, such as the neutrophil/HDL ratio (NHR), lymphocyte/HDL ratio (LHR), monocyte/HDL ratio (MHR), and platelet/HDL ratio (PHR), have recently been introduced as novel markers of inflammation. These ratios have been proposed as potential indicators of systemic inflammation and oxidative stress under various inflammatory conditions [16, 17]. Studies have identified a strong association between these ratios and the onset and prognosis of cardiovascular diseases, Parkinson's disease, and certain physical health conditions [16, 17].

Although studies investigating these ratios in psychiatric conditions are scarce, a retrospective analysis of individuals with severe mental illnesses demonstrated significant differences in NHR, LHR, MHR, and PHR values in those with bipolar disorder (BD) compared to healthy subjects. Considering the intricate relationships among neutrophils, lymphocytes, monocytes, platelets, and HDL, a composite marker incorporating NHR, LHR, MHR, and PHR may offer a more comprehensive assessment of inflammation levels than individual metrics. However, in cardiovascular conditions, TG levels have been predominantly accepted as an independent risk factor in various studies [18]. For this reason, the atherogenic index of plasma (AIP), which is thought to be a more objective indicator of atherosclerosis, was introduced. AIP was calculated as the logarithm of the ratio of plasma triglyceride (TG) level to high-density lipoprotein (HDL) level with base 10 [log (TG/HDL) ratio]. AIP reflects the balance between protective and atherogenic lipoproteins [19]. Recently,

https://doi.org/10.5455/annalsmedres.2025.01.019

AIP has been reported to be a good marker for the early detection of subclinical cardiovascular disease in diseases characterized by chronic inflammation, such as Behçet's disease and ankylosing spondylitis [20, 21]. There are also a few studies on BD [22, 23].

Although there are many biomarkers indicating inflammation, since these biomarkers require additional financial resources, we believe that it is more valuable to detect biomarkers that can be obtained during routine examinations.

When we look at the literature, studies on BD have many limitations, especially regarding the use of drugs, and only the acute phases of the disease have been addressed.

It is thought that there is still a need to define specific and sensitive markers that can show that the inflammatory process in BD changes during the disease, during remission, and during manic episodes, especially biomarkers that are easily measurable, cost-effective, and reproducible, reflect the dynamism and clinical progression of the disease, and are easy to interpret by clinicians.

In our study, we aimed to examine whether the hemogram and biochemical parameters of patients with BD in the remission and manic episode periods and healthy controls, who were included in the study with strict exclusion criteria especially related to drug use and even naive manic episode patients were included to observe the effects of drug use, whether a difference that could be a biomarker could be detected from these parameters, and to evaluate the relationship between clinical variables and these parameters.

MATERIALS AND METHODS

Procedure

Our study focused on the retrospective comparison of the clinical, hemogram, and biochemical parameters of three groups: patients in remission and manic episodes who applied to the Erzurum City Hospital Psychiatry Outpatient Clinic between December 2023 and December 2024, who were diagnosed with BD Type 1 according to DSM-5 diagnostic criteria, and controls who applied to the psychiatry outpatient clinic for reporting purposes (starting work, single physician's report reporting status). Outpatient clinic and clinic records will be used to obtain the data of patients and controls included in the study.

The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Health Sciences University Erzurum Faculty of Medicine Scientific Research Ethics Committee with the decision numbered BAEK 2024/12-215.

Research sample

Criterion sampling, a purposive sampling method, was used in our study [24]. This sampling type is based on samples that meet certain predetermined criteria. The criteria determined by the researcher to explain the situations examined can be used for this type of sampling. In criterion sampling, the individuals planned to be included in the study are determined according to certain criteria. The criteria or criteria used can be created by the researcher, or a previously prepared list of criteria can be used. For our study, the data of all patients with BD type 1 who applied to our outpatient clinic within the specified date intervals were evaluated. Patients who did not meet the inclusion criteria were excluded, and a sample was formed. Healthy controls were selected from those who applied to our outpatient clinic to confirm that they were healthy. When their health records and interviews were examined, it was determined that they had not previously consulted a psychiatrist and had no known chronic or acute physical or mental illness. When the hospital records were examined, it was confirmed that the person did not have any psychopathology as a result of the current mental status examination and psychometric evaluations. The inclusion criteria for participants who were evaluated in the psychiatry outpatient clinic in the desiganted period are summarized in Table 1.

A flow diagram illustrating the recruitment process is summarized in Figure 1.

Data collection tools

Sociodemographic and Clinical Data Form: Medical records of all participants were analyzed. Characteristics such as age, height, weight, BMI, and number of episodes were obtained from hospital records.

Hamilton Depression Scale: This scale is not diagnostic but is used to measure the severity of depression. The test is formed on a three- and five-point Likert scale. Turkish validity and reliability studies were conducted [26].

The Young Mania Rating Scale (YMRS): It is used to determine the severity of a manic episode. The test is constructed on a five-point likert scale. A high score indicates that mania is severe. A Turkish validity and reliability study was conducted [27].

Complete blood count and biochemical analysis

Blood analyses were performed in the biochemistry laboratory using an automated hematological analyzer (Sysmex XN-1000) and a biochemistry analyzer (Atellica, siemens Healthineers).

Normal reference ranges are as follows: neutrophils, 1,8-6,98×10^9 /L: lymphocytes, 1,21-3,77×10^9 /L; monocytes, 0,29-0,95×10^9 /L; platelets, 152-383×10^9 /L; HDL, 35-55 mg/dL; LDL, 100-129 mg/dL; triglycerides, 0-200 mg/dL; total cholesterol, 0-200 mg/dL; and CRP, 0-5 mg/L.

The indexes used in our study were calculated using the following formulas:

NHR = neutrophil/HDL ratio; MHR = monocyte/HDL ratio; LHR = lymphocyte/HDL ratio; PHR = platelet/HDL ratio.

https://doi.org/10.5455/annalsmedres.2025.01.019

Table 1. Comparison of sociodemographic data, clinical results, blood parameters and calculated indices of the groups.

	Control N:70 Mean±SD	Remission N:66 Mean±SD	Manic episode N:67 Mean±SD	χ^2 /F value	p value
Age	38.14	39.33	31.61	9.151	p<0.001
Gender				1.522	0.467
Women	26	30	24		
Men	44	36	43		
Marital Status				10.628	0.00
Single	28	42	43		
Married	42	24	24		
Smoking Status				10.782	5.005
No	42	48	30		
Yes	28	18	37		
Alcohol Use Status				9.118	0.010
No	62	66	58		
Yes	8	15	9		
BMI	25.11	28.29	26.60	26.899	p<0.001
Duration of disease(year)	-	13.42±6.32	8.46±10.38	3.328	0.001
Number of Episodes	-	6.03±2.91	4.70±4.57	1.999	0.048
Number of Manic Episodes	-	3±1.54	2.40±1.73	2.094	0.038
Number of Depressive Episodes	-	3.03±1.43	1.89±2.32	3.387	0.001
Neutrophil count x 10^9/ L	3.90±1.42	4.81±1.94	6.29±1.49	37.299	p<0.001
Monocyte count x 10^9/ L	0.59±0.13	0.60±0.19	0.76±0.25	16.192	p<0.001
Lymphocyte count x 10^9/ L	2.28±0.59	2.62±0.83	2.21±0.74	6.247	p<0.001
Platelet count x 10^9/ L	54.92±6.56	95.53±11.75	71.20±4.99	0.208	0.813
CRP (mg/L)	2.66±2.06	3.47±3.00	5.28±4.54	10.893	.000
Triglyceride (mmol/L)	1.26±0.58	1.84±0.81	1.57±0.79	10.375	p<0.001
Total Cholesterol (mmol/L)	4.52±0.94	4.31±0.66	3.88±0.90	9.875	p<0.001
HDL (mmol/L)	1.05±0.26	0.99±0.38	1.07±0.35	0.931	0.396
LDL (mmol/L)	3.23±0.93	3.04±0.55	2.83±1.02	3.634	0.028
NHR	3.93±1.79	5.45±3.19	6.48±2.55	17.107	p<0.001
MHR	0.60±0.21	0.67±031	0.81±0.42	7.883	0.001
LHR	2.33±0.97	2.88±1.14	2.43±1.29	4.473	0.013
PHR	272.64±80.21	291.79±127.54	285.36±116.69	0.541	0.583
AIP	0.041±0.26	0.24±0.27	0.12±0.33	8.219	p<0.001
PIV	289.22±151.43	387.35±342.95	444.41±338.04	28.324	p<0.001
IBI	5.46±7.43	6.81±6.48	17.56±18.73	19.978	p<0.001

BMI: Body mass index, CRP:C-reactive protein, NHR:Neutrophil/HDL ratio, LHR:Lymphocyte/HDL ratio, MHR:Monocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, SD: Standard Deviation, N: number of participants, χ^2: Chi-square, F: one-way ANOVA test value, p<0.05: statistical significance level.

PIV = Neutrophil (10^9/L) × Platelet (10^9/L) × Monocyte (10^9/L)/Lymphocyte (10^9/L).

IBI = CRP × Neutrophil/Lymphocyte.

AIP: $\log_{10}$(TG/HDL).

Statistical analysis

Statistical analyses were performed using the Statistical software Package for Social Sciences version 26 (SPSS Statistics version 26.0) (IBM, Armonk, USA). Descriptive statistics, including means, standard deviations, and frequencies, were calculated. Normality was assessed by examining skewness and kurtosis values, with all variables falling within the acceptable range of -2 to +2. Categorical variables were analyzed using the chi-square test. For comparisons between two independent groups meeting normality assumptions, the independent samples t-test was employed. Comparisons involving more than two independent groups with normally distributed data were conducted using one-way ANOVA. Where ANOVA yielded significant results, post hoc comparisons were performed using the Bonferroni test for equal variances and Tamhane's T2 test for unequal variances. The relationship between quantitative variables was assessed using Pearson's correlation coefficient. Binary logistic regression analysis was used to identify significant predictors of the dependent variable. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic utility of continuous variables and to determine appropriate cut-off values. A p-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

The study included data from 66 patients with BD in remission, 67 patients with a manic episode, and 70 healthy controls. In the manic episode group, 32 patients experi-

https://doi.org/10.5455/annalsmedres.2025.01.019

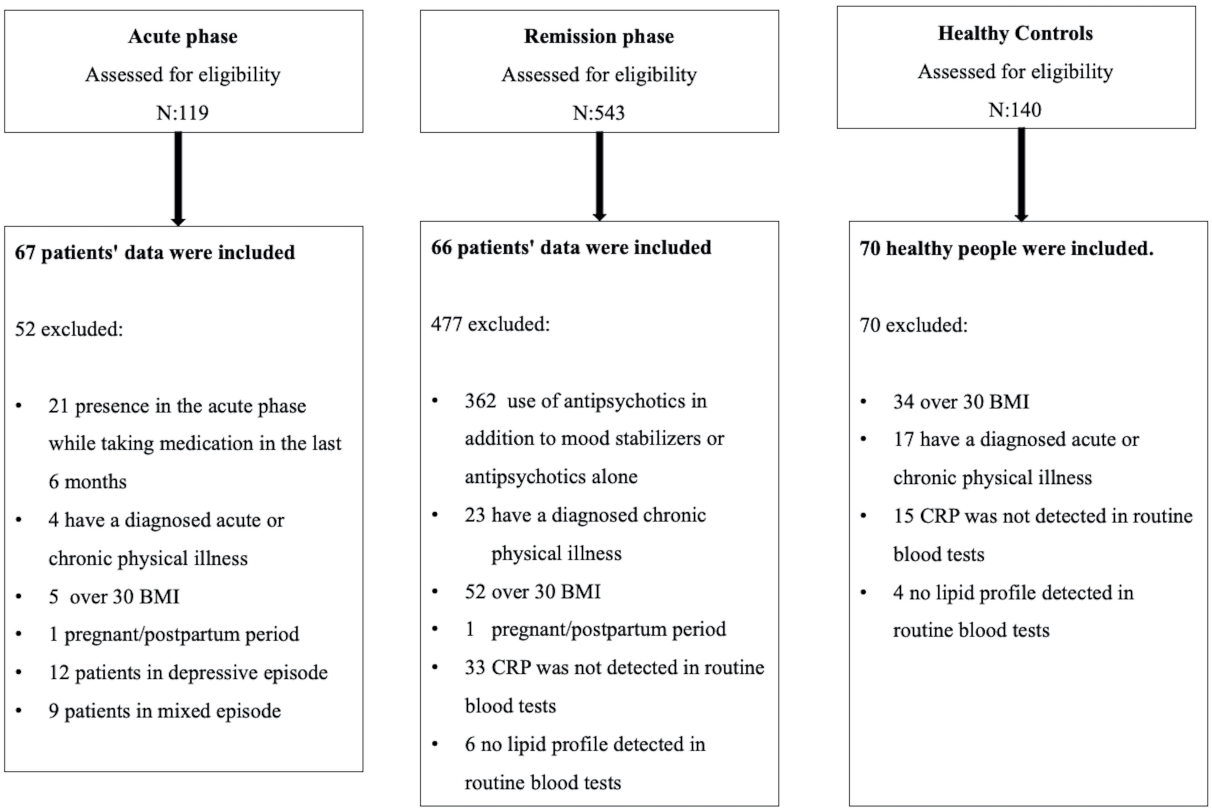

Figure 1. A flow diagram summarizing the recruitment procedures.

Table 2. Posthoc analysis results of calculated indices.

	p value		
	Control-Remission	Control-Manic Episode	Manic Episode-Remission
NHR	0.003	p<0.001	0.126
MHR	0.326	0.001	0.072
LHR	0.009	0.944	0.98
PHR	0.657	0.843	0.987
AIP	0.045	0.051	0.052
PIV	0.103	p<0.001	p<0.001
IBI	0.593	p<0.001	p<0.001

NHR:Neutrophil/HDL ratio, LHR:Lymphocyte/HDL ratio, MHR: Monocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index.

enced their first manic episode and had not received psychiatric treatment before the study. Of the 66 patients in remission, 35 were on sodium valproate+valproic acid, 23 received lithium carbonate, and 8 received both lithium carbonate and sodium valproate+valproic acid. The drug blood levels of patients using sodium valproate+valproic acid were approximately 60-80 μg/mL, whereas the drug blood levels of patients using lithium carbonate were between 0.6 and 0.8 mEq/L.

The sociodemographic data, blood parameters, calculated indices, and clinical characteristics of the patients are presented in Table 1. The manic episode group had significantly lower age, illness duration, and number of episodes compared to the remission group (p: <0.001, <0.001, 0.001, respectively), as it included patients in their first episode. Significant differences in the calculated indices (NHR, MHR, LHR, AIP, PIV, IBI) were observed among the three groups (p values: <0.001, 0.001, 0.013, <0.001, <0.001, <0.001, respectively). Post hoc analyses for the indices are presented in Table 2. NHR was significantly lower in the control group compared with both the manic episode and remission groups (p: <0.001, 0.003). MHR was significantly higher in the manic episode group compared with the control group (p: 0.001). LHR and AIP were higher in the remission group than in the control group (p: 0.009 and 0.045). PIV and IBI values were significantly higher in the manic episode group compared with both the

Table 3. Comparison of indices calculated from blood parameters of bipolar disorder patients with drug naive first manic episode and recurrent manic episode.

	First manic episode, drug-naïve	Manic Episode	t	p
NHR	7.35±3.03	5.67±1.71	-2.758	0.008
MHR	0.94±0.48	0.70±031	-2.424	0.019
LHR	2.87±1.30	2.02±1.16	-2.808	0.007
PHR	322±137.48	251.87±82.34	-2.504	0.016
AIP	0.21±0.32	0.04±0.32	-2.095	0.040
PIV	590.88±212.73	728.49±455.09	1.607	0.114
IBI	12.03±12.93	22.61±21.76	2.388	0.020

NHR:Neutrophil/HDL ratio, LHR:Lymphocyte/HDL ratio, MHR: Monocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, t: independent samples t-test, p<0.05: statistical significance level.

https://doi.org/10.5455/annalsmedres.2025.01.019

Table 4. Correlation of clinical characteristics and laboratory results in patients with Bipolar Disorder.

		Age	BMI	DOD	NOE	NDE	NME	NHR	MHR	LHR	PHR	AIP	PIV	IBI
Age	r	1	0.278**	0.757**	0.545**	0.582**	0.540**	0.013	-0.138	-0.060	0.115	0.146	0.002	0.036
	p		0.001	0.000	0.000	0.000	0.000	0.879	0.114	0.490	0.187	0.093	0.981	0.679
BMI	r		1	.178*	0.015	0.040	0.059	0.478**	0.461**	0.506**	0.538**	0.435**	0.138	0.013
	p			0.040	0.867	0.648	0.498	0.000	0.000	0.000	0.000	0.000	0.113	0.886
DOD	r			1	.804**	0.827**	0.768**	-0.069	-0.188*	-0.208*	-0.052	0.010	0.134	0.181*
	p				0.000	0.000	0.000	0.431	0.030	0.016	0.554	0.905	0.124	0.037
NOE	r				1	0.960**	0.958**	0.009	-0.112	-0.257**	-0.043	-0.047	0.256**	0.275**
	p					0.000	0.000	0.916	0.199	0.003	0.626	0.591	0.003	0.001
NDE	r					1	0.925**	-0.037	-0.159	-0.204*	-0.018	-0.035	0.111	0.203*
	p						0.000	0.674	0.067	0.019	0.833	0.693	0.202	0.019
NME	r						1	0.046	-0.104	-0.217*	0.009	-0.008	0.210*	0.177*
	p							0.597	0.233	0.012	0.919	0.930	0.015	0.042
NHR	r							1	0.809**	0.469**	0.770**	0.529**	0.539**	0.100
	p								0.000	0.000	0.000	0.000	0.000	0.250
MHR	r								1	0.612**	0.610**	0.566**	0.367**	0.126
	p									0.000	0.000	0.000	0.000	0.149
LHR	r									1	0.586**	0.650**	-0.252**	-0.280**
	p										0.000	0.000	0.003	0.001
PHR	r										1	0.637**	0.279**	-0.150
	p											0.000	0.001	0.085
AIP	r											1	-0.063	-0.250**
	p												0.470	0.004
PIV	r												1	0.443**
	p													0.000
IBI	r													1

*BMI: Body mass index, NHR:Neutrophil/HDL ratio, LHR:Lymphocyte/HDL ratio, MHR:Monocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, **. Correlation is significant at the 0.01 level.*. Correlation is significant at the 0.05 level., DOD: Duration of Disease, NOE: Number of Episodes, NDE: Number of Depressive Episodes, NME: Number of Manic Episodes*

Table 5. Predictive Factors for Manic Episode- Logistic Regression Bacward Conditional Model.

	Variables in the Equation	B	S.E.	p	Exp(B)	95% CI for EXP(B) Lower	Upper
Step 1	LHR	-1.486	14.135	0.916	0.226	0.000	25.318
	PHR	0.019	0.124	0.881	1.019	0.799	1.299
	AIP	-0.605	1.021	0.553	0.546	0.074	4.041
	IBI	0.080	0.028	0.005	1.084	1.025	1.146
	PIV	0.003	0.001	0.012	1.003	1.001	1.005
	Age	-0.045	0.038	0.241	0.956	0.888	1.030
	Duration of disease	-0.097	0.044	0.027	0.907	0.832	0.989
	Constant	0.796	1.155	0.490	2.217	-	-
Step 5	IBI	0.094	0.027	0.000	1.099	1.042	1.159
	PIV	0.002	0.001	0.001	1.002	1.001	1.004
	Duration of disease	-0.137	0.031	0.000	0.872	0.820	0.927
	Constant	-0.709	0.428	0.098	0.492	-	-

LHR:Lymphocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, p<0.05:Statistical significance level.

https://doi.org/10.5455/annalsmedres.2025.01.019

Table 6. Bipolar Disorder remission -manic episod ROC analysis results.

Area Under the Curve								
				Asymptotic 95% Confidence Interval				
Predictor	Area	Std. Error	p value	lower bound	upper bound	Cutoff value	Sensivity	Specifiicty
LHR	0.401	0.051	0.048	0.301	0.500	-	-	-
PHR	0.501	0.051	0.982	0.401	0.601	-	-	-
AIP	0.411	0.050	0.077	0.314	0.508	-	-	-
IBI	0.722	0.043	p<0.001	0.637	0.807	6.93	64.2%	66.7%
PIV	0.742	0.045	p<0.001	0.654	0.830	407.89	74.6%	69.7%

LHR:Lymphocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, p<0.05: Statistical significance level.

Table 7. Bipolar disorder patient-control ROC analysis results.

Area Under the Curve								
				Asymptotic 95% Confidence Interval				
Predictor	Area	Std. Error	Asymptotic Sig.	lower bound	upper bound	Cutoff value	Sensivity	Specifiicty
LHR	0.565	0.041	0.130	0.484	0.645	-	-	-
PHR	0.510	0.040	0.819	0.431	0.588	-	-	-
AIP	0.639	0.039	0.001	0.562	0.716	0.85	62.4%	60%
IBI	0.678	0.038	p<0.001	0.603	0.753	4.37	63.9%	65.7%
PIV	0.673	0.037	p<0.001	0.601	0.746	293.55	65.4%	68.6%

LHR:Lymphocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, p<0.05: Statistical significance level.

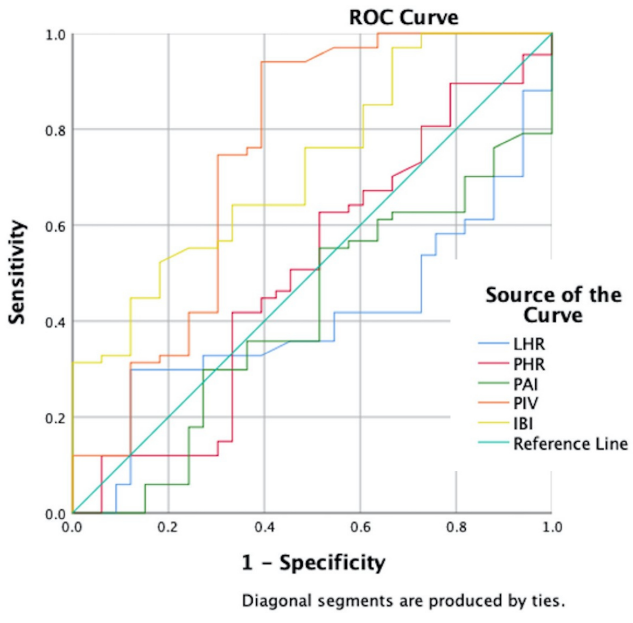

Figure 2. ROC analysis for distinguishing between manic episodes.

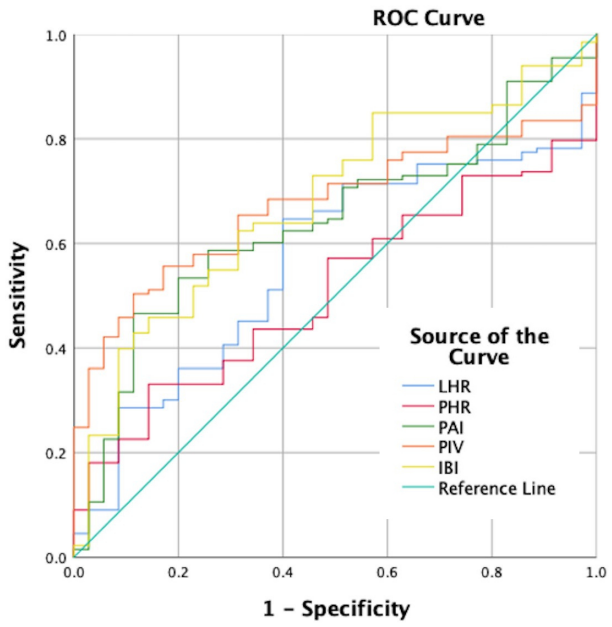

Figure 3. ROC analysis for distinguishing bipolar disorder.

remission and control groups (p<0.001 for both).

The calculated indices were also compared between patients with first manic episodes who were not taking medication and those with recurrent manic episodes. Significant differences were found in NHR (p: 0.008), MHR (p: 0.019), LHR (p: 0.007), and AIP (p: 0.040), all higher in patients with first manic episode. IBI (p: 0.020) was higher in patients with recurrent episodes, whereas PIV (p: 0.114) showed no signifi-

https://doi.org/10.5455/annalsmedres.2025.01.019

cant difference between the two groups (Table 3).

A correlation analysis was performed to examine the relationship between clinical characteristics and calculated blood indices. IBI was positively correlated with illness duration, number of manic episodes, number of depressive episodes, and total number of episodes. PIV was positively correlated with the number of manic episodes and total episodes. AIP showed a positive correlation with BMI, and LHR was positively correlated with BMI, illness duration, and the number of manic and depressive episodes (Table 4).

Additionally, a correlation analysis was conducted between the Young Mania Rating Scale (YMRS) score and calculated blood indices in the manic episode group. Positive correlations were found between the YMRS score and NHR (r: 0.294, p: 0.016), MHR (r: 0.334, p: 0.006), PIV (r: 0.375, p: 0.002), and IBI (r: 0.380, p: 0.002).

Binary logistic regression (Backward Conditional Model) was used to identify the predictors of episodes of manic episodes. The presence of a manic episode was the dependent variable, and age, illness duration, LHR, PHR, AIP, IBI, and PIV were independent variables (Table 5). Due to multi-collinearity, the number of episodes and other related variables was excluded. IBI ($p<0.001$) and PIV (p: 0.001) were identified as positive predictors of manic episodes, whereas illness duration was a negative predictor. A one-unit increase in IBI or PIV doubled the risk of a manic episode (OR: 1.099 and 1.002, respectively), whereas a one-year increase in illness duration reduced the likelihood of a manic episode by 0.8 times (OR: 0.872) (Table 6). The risk of manic episodes decreased as the illness duration increased.

ROC analysis was conducted to evaluate the potential of LHR, PHR, AIP, IBI, and PIV values in distinguishing manic episodes in BD and to establish cutoff values. IBI and PIV were found to be useful for diagnosing manic episodes in BD, with cut-off values of 6.93 for IBI and 407.84 for PIV (Figure 2, Table 6). Additionally, ROC analysis for BD differentiation revealed that AIP, IBI, and PIV values above 0.85, 4.37, and 293.55, respectively, were effective in identifying bipolar disorder (Figure 3, Table 7).

DISCUSSION

This study examined the relationship between NHR, MHR, LHR, PHR, AIP, PIV, and IBI, which are evaluated together with blood cell count and biochemical parameters as inflammatory, immunonutritive, and cardiovascular markers, and BD periods and severity of manic episodes. In this study, the primary endpoints were NHR, MHR, LHR, AIP, PIV, and IBI. Blood parameters included neutrophils, monocytes, lymphocytes, platelets, HDL, TC, LDL, and TG, which were used along with these calculated indices. Clinical features included disease duration, number of episodes, BMI, and YMRS score. Correlation analyses were conducted to examine the relationships between clinical features and the calculated indices, while binary logistic regression was utilized to determine the predictors of manic episodes. Receiver operating characteristic (ROC) analyses were conducted to evaluate the potential of LHR, PHR, AIP, IBI, and PIV in distinguishing manic episodes.

As expected, PIV and IBI were highest during the episodes, and these two values were found to be associated with manic episodes. Although there are many studies in terms of BD inflammation, to the best of our knowledge, there is no study evaluating BD periods and severity in terms of PIV and IBI. In a recent meta-analysis study, CRP levels were higher in patients in the manic period than in healthy controls and patients in depressive and euthymic states [6]. While there are studies showing increased neutrophil and lymphocyte counts in patients with BD compared with controls [28], there are also studies in which no significant difference was found [7]. Again, in a study including 78 patients with manic and 88 remission period BD and 101 controls, the monocyte/lymphocyte ratio was found to be high in the manic episode, while no significant results were found in terms of platelet/lymphocyte and neutrophil/lymphocyte ratio [29]. Although it is difficult to compare these findings with our study results, they are consistent with studies showing inflammation in BD and especially in manic episodes. In the same study, the lipid profile was also examined, and triglyceride, LDL, and total cholesterol levels were found to be higher in the remission group, whereas HDL levels did not show a significant difference [29]. Inflammation during manic episodes may be a reflection of physiological stress and metabolic changes. Insomnia, excessive activity, high energy levels, and increased cortisol and sympathetic nervous system activation during manic episodes may be factors that trigger this inflammation.

In our study, AIP was significantly higher in the remission period. This was an expected finding due to the atherogenetic effect of long-term medications, eating patterns, and sedentary lifestyles of the patients [30]. In a study conducted by Kalelioğlu et al. with 68 patients with manic attack, it was shown that while pre-treatment AIP values were similar to healthy controls, post-treatment AIP values increased significantly compared with pre-treatment values. This was interpreted as that even short-term treatments may increase cardiogenic risk, that the manic period may have a positive effect on atherogenic risk or at least that it would not have any effect [23]. Although only patients in the remission period who were using mood stabilizers and not antipsychotics were included in our study, AIP values were significantly higher than those of the control group. AIP was significantly higher in patients with a naive first manic episode. This finding suggests that people who are predisposed to this disease are also structurally more vulnerable to atherogenicity regardless of the drug. In a review of 142 studies evaluating metabolism and cardiovascular diseases in BD, mortality rates from cardiovascular disease and pulmonary embolism doubled compared with the general population. Reduced exercise and poor diet, frequent depressive episodes, comorbidity with substance abuse, and poor

https://doi.org/10.5455/annalsmedres.2025.01.019

quality general medical care may contribute to the additional risk of these medical problems in people with bipolar disorder. Contrary to popular belief, long-term treatment with lithium, antipsychotics, and tricyclic antidepressants may reduce overall mortality [31]. These findings suggest that there are mixed results regarding cardiovascular risk in patients with BD and that conflicting results may have been found because this may be related to many factors such as ethnic origin, drugs used, anti-inflammatory effects of drugs, genetic predispositions, sedentary lifestyle, and predisposition to drugs and smoking.

Although LHR was significantly higher in the remission period, MHR was significantly higher in the attack period, and NHR was significantly lower in the control group, the ratio of these leukocytes to HDL did not have a predictive effect on disease or attack period. NHR was weakly correlated, and MHR was strongly correlated with the severity of the attack, determined by YMRS only during the attack period. Again, PIV and IBI showed a strong relationship and positive correlation with attack severity. Although no study has compared PIV and IBI one-to-one, the relationship between CRP and YMRS was examined in a study conducted by Kara et al. with 35 patients in the manic period, but no relationship was found [32]. In a study conducted with 116 patients with BD using high-sensitive CRP, which was thought to be more specific for inflammation, a positive correlation was found between YMRS scores and number of attacks and high-sensitive CRP levels [33]. In the present study, IBI was higher in patients with recurrent attacks. IBI increased as the disease duration and the number of episodes increased, whereas PIV increased as the number of episodes, especially manic episodes, increased.

In our study, PIV and IBI were associated with both a manic episode and illness. AIP was also shown to be associated with illness. Patients who were not taking medication during the episode were included; however, patients in remission were taking mood stabilizers. Studies are showing the antiinflammatory effects of mood stabilizers [34]. However, PIV, IBI, and AIP were associated with both inflammation and atherogenicity were high in patients in remission. These findings suggest that the disease is inherently an inflammatory process, although the mechanism of this inflammation has not been fully elucidated.

Our study has some strengths and limitations. The fact that our study sample included patients with a first episode manic episode who had never taken any medication, that those in manic episode were not taking medication for the last 6 months, and that patients in remission were only taking mood stabilizers strengthens our study in terms of reducing the limitation of medication use. In addition, the fact that patients with a BMI >30 were not included in the study due to its effect on both inflammation and atherogenicity, and other strict inclusion criteria, strengthens our study. Confounding factors that may have an impact on inflammatory states, such as sleep, exercise, nutrition, alcohol consumption, smoking status, and lifestyle, were not included in the analysis. Since the manic episode group included patients with their first episode, the age of this group was lower than that of the other two groups. Although the effect of age was controlled in the logistic regression analysis, another limitation is that the ages of the groups were not similar. Although we tried to minimize the effect of drugs on inflammation, the fact that patients in the remission period were taking mood stabilizers, and these drugs have known anti-inflammatory effects, is also a limitation of our study. The fact that inflammation indicators are still high, although patients in the remission period are using drugs known to have anti-inflammatory effects, suggests that there may also be the effect of factors such as alcohol, smoking, and lifestyle changes, which we cannot exclude as a confounding effect in this group of patients. The retrospective and cross-sectional design of the study is an important limitation. This approach prevents the establishment of strong causal relationships between blood parameters, biomarkers, and disease-related outcomes. In addition, differences in the timing of blood collection and whether blood was drawn under appropriate conditions (such as fasting and postprandial) may have caused variations in some parameters (such as lipids). Although strict inclusion and exclusion criteria were applied in this study, since the data were obtained from hospital records, treatments and disease diagnoses not included in hospital records may have been missed. The administration of YMRS to participants by different psychiatrists is both a limitation and an advantage. This may have prevented possible bias. Evaluation of inflammatory and atherogenic parameters in the same patients before the first episode, during the episodes, and during the remission period; analyzing these parameters by detailing the confounding factors will provide more accurate data and can be planned for future longitudinal studies.

Given the inflammatory and atherogenic processes involved in the etiopathogenesis, the novel biomarkers PIV, IBI, and AIP may be promising therapeutic targets for BD. In addition, these biomarkers can be used as easily accessible, inexpensive clinical tools to predict disease, manic episodes, and the severity of manic episodes. Given the limitations of our study, further validation is needed to confirm the clinical validity of our results. Therefore, prospective follow-up of these groups is important to assess progress in the patient and control groups. Longitudinal and well-designed studies involving larger patient groups should be conducted to ensure the results of the study are generalizable. It should be noted that in this study, which aims to reflect a real-world sample of the population, our results may not be representative of the entire population.

https://doi.org/10.5455/annalsmedres.2025.01.019

Ethics Committee Approval: This study was approved by the Health Sciences University Erzurum Faculty of Medicine Scientific Research Ethics Committee with the decision numbered BAEK 2024/12-215.

Peer-review: Externally peer-reviewed.

Informed Consent: Informed consent was not obtained due to the retrospective design of the study.

Financial Disclosure: No financial support was received for the research, writing, and/or publication of this article.

REFERENCES

1. Ferrari AJ, Baxter AJ, Whiteford HA. A systematic review of the global distribution and availability of prevalence data for bipolar disorder. *J Affect Disord.* 2011;134(1-3):1-13. doi: 10.1016/j.jad.2010.11.007.
2. Leboyer M, Soreca I, Scott J, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? *J Affect Disord.* 2012;141(1):1-10. doi: 10.1016/j.jad.2011.12.049.
3. Cremaschi L, Kardell M, Johansson V, et al. Prevalences of autoimmune diseases in schizophrenia, bipolar I and II disorder, and controls. *Psychiatry Res.* 2017;258:9-14. doi: 10.1016/j.psychres.2017.09.071.
4. Bulut NS, Yorguner N, Carkaxhiu Bulut G. The severity of inflammation in major neuropsychiatric disorders: comparison of neutrophil-lymphocyte and platelet-lymphocyte ratios between schizophrenia, bipolar mania, bipolar depression, major depressive disorder, and obsessive compulsive disorder. *Nord J Psychiatry.* 2021;75(8):624-32. doi: 10.1080/08039488.2021.1919201.
5. Clyne B, Olshaker JS. The C-reactive protein. *J Emerg Med.* 1999;17(6):1019-25. doi: 10.1016/S0736-4679(99)00135-3.
6. Fernandes BS, Steiner J, Molendijk ML, et al. C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry.* 2016;3(12):1147-56. doi: 10.1016/S2215-0366(16)30370-4.
7. Fucà G, Guarini V, Antoniotti C, et al. The Pan-Immune-Inflammation Value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the Valentino and TRIBE first-line trials. *Br J Cancer.* 2020;123(3):403-9. doi: 10.1038/s41416-020-0894-7.
8. Murat B, Murat S, Ozgeyik M, Bilgin M. Comparison of pan-immune-inflammation value with other inflammation markers of long-term survival after ST-segment elevation myocardial infarction. *Eur J Clin Investig.* 2023;53(1):e13872. doi: 10.1111/eci.13872.
9. Lee LE, Ahn SS, Pyo JY, et al. Pan-immune-inflammation value at diagnosis independently predicts all-cause mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis. *Clin Exp Rheumatol.* 2021;39(2):S88-S93.doi: 10.55563/clinexprheumatol/m46d0v.
10. Xie H, Ruan G, Ge Y, et al. Inflammatory burden as a prognostic biomarker for cancer. *Clin Nutr.* 2022;41(6):1236-43. doi: 10.1016/j.clnu.2022.04.019.
11. Gürbüzer N, Ozkaya AL. Inflammatory Burden Index (IBI) and Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score in Alzheimer's Disease: A Retrospective Comparative Study. *Cureus.* 2024;16(9):e69148. doi: 10.7759/cureus.69148.
12. Kumeda Y, Inaba M, Goto H, et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. *Arthritis Rheum.* 2002;46(6):1489-97. doi: 10.1002/art.10269.
13. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. *Eur Heart J.* 2017;38(32):2459-72. doi: 10.1093/eurheartj/ehx144.
14. Zimetti F, Adorni MP, Marsillach J, et al. Connection between the Altered HDL Antioxidant and Anti-Inflammatory Properties and the Risk to Develop Alzheimer's Disease: A Narrative Review. *Oxid Med Cell Longev.* 2021;2021(1):6695796. doi: 10.1155/2021/6695796.
15. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. *Nat Rev Immunol.* 2015;15(2):104-16. doi: 10.1038/nri3793.
16. Huang J-B, Chen Y-S, Ji H-Y, et al. Neutrophil to high-density lipoprotein ratio has a superior prognostic value in elderly patients with acute myocardial infarction: a comparison study. *Lipids Health Dis.* 2020;19:1-12. doi: 10.1186/s12944-020-01238-2
17. Liu Z, Fan Q, Wu S, et al. Compared with the monocyte to high-density lipoprotein ratio (MHR) and the neutrophil to lymphocyte ratio (NLR), the neutrophil to high-density lipoprotein ratio (NHR) is more valuable for assessing the inflammatory process in Parkinson's disease. *Lipids Health Dis.* 2021;20:1-12. doi: 10.1186/s12944-021-01462-4.
18. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation.* 2011;123(20):2292-333. doi: 10.1161/CIR.0b013e3182160726.
19. Ross R. Atherosclerosis-an inflammatory disease. *N Engl J Med.* 1999;340(2):115-26. doi: 10.1056/NEJM199901143400207.
20. Cure E, Icli A, Uslu AU, et al. Atherogenic index of plasma: a useful marker for subclinical atherosclerosis in ankylosing spondylitis: AIP associate with cIMT in AS. *Clin Rheumatol.* 2018;37:1273-80. doi: 10.1007/s10067-018-4027-0.
21. Cure E, Icli A, Ugur Uslu A, et al. Atherogener Plasma-Index könnte ein starker Prädiktor für subklinische Atherosklerose bei Patienten mit M. Behçet sein. *Z Rheumatol.* 2017;76:259-66. doi: 10.1007/s00393-016-0141-z.
22. Nunes SOV, de Melo LGP, de Castro MRP, et al. Atherogenic index of plasma and atherogenic coefficient are increased in major depression and bipolar disorder, especially when comorbid with tobacco use disorder. *J Affect Disord.* 2015;172:55-62. doi: 10.1016/j.jad.2014.09.038.
23. Kalelioglu T, Genc A, Karamustafalioglu N, Emul M. Assessment of cardiovascular risk via atherogenic indices in patients with bipolar disorder manic episode and alterations with treatment. *Diabetes Metab Syndr.* 2017;11:S473-S5. doi: 10.1016/j.dsx.2017.03.038.
24. Panacek EA, Thompson CB. Sampling methods: Selecting your subjects. *Air Med J.* 2007;26(2):75-8. doi: 10.1016/j.amj.2007.01.001.
25. Hirschfeld RM, Calabrese JR, Frye MA, et al. Defining the clinical course of bipolar disorder: response, remission, relapse, recurrence, and roughening. *Psychopharmacol Bull.* 2007;40(3):7-14.
26. Akdemir A, Örsel DS, Dağ İ, et al. Hamilton depresyon derecelendirme ölçeği (HDDÖ)'nin geçerliliği-güvenirliliği ve klinikte kullanımı. *3P Dergisi*. 1996;4(4):251-9.
27. Karadağ F, Oral ET, Aran Yalçın F, Erten E. Young mani derecelendirme ölçeğinin Türkiye'de geçerlik ve güvenilirliği. *Turk Psikiyatri Derg.* 2001;13(2):107-14.
28. Garip B, Oğur B, Tekin Ş, İnanç Ö. Comparative Study of Inflammatory Markers in Schizophrenia, FirstEpisode Psychosis, and Bipolar Disorder. *Genel Tip Dergisi.* 2024;34(5):624-8. doi: 10.54005/geneltip.1413078.
29. Ekinci O, Erkan Ekinci A. Inflammatory parameters and blood lipid values across the different mood states in patients with bipolar disorder. *Turkish J Clin Psychiatry.* 2020;23(4):414-22. doi: 10.5505/kpd.2020.98216.
30. Chaggar PS, Shaw SM, Williams SG. Effect of antipsychotic medications on glucose and lipid levels. *J Clin Pharmacol.* 2011;51(5):631-8. doi: 10.1177/0091270010368678.
31. Morriss R, Mohammed FA. Metabolism, lifestyle and bipolar affective disorder. *J Psychopharmacol.* 2005;19(6_suppl):94-101. doi: 10.1177/0269881105058678.
32. Kara A, Balaban ÖD, Çınar B, et al. Bipolar Manide Enflamasyon Belirteci Olarak High Mobility Grup 1 Protein. *Noro Psikiyatr Ars.* 2024;61(2):160–6. doi: 10.29399/npa.28599.

https://doi.org/10.5455/annalsmedres.2025.01.019

33. Queissner R, Fellendorf FT, Dalkner N, et al. The influence of chronic inflammation on the illnesscourse of bipolar disorder: A longitudinal study. *J Psychiatr Res.* 2024;174:258-62. doi: 10.1016/j.jpsychires.2024.04.024.

34. Leu SJ, Yang YY, Liu HC, et al. Valproic acid and lithium meditate anti-inflammatory effects by differentially modulating dendritic cell differentiation and function. *J Cell Physiol.* 2017;232(5):1176-86. doi: 10.1002/jcp.25604.

https://doi.org/10.5455/annalsmedres.2025.01.019

Ann Med Res

Current issue list available at Ann Med Res

Annals of Medical Research

journal page: annalsmedres.org

Evaluating peripapillary choroidal vascularity index and peripapillary retinal nerve fiber layer thickness in patients with retrobulbar optic neuritis: A comparative study

Hidayet Sener [a],*, Hatice Kubra Sonmez [a]

[a]Erciyes University, Faculty of Medicine, Department of Ophthalmology, Kayseri, Türkiye
*Corresponding author: hidayetsener00@gmail.com (Hidayet Sener)

MAIN POINTS

- The posterior tibial curvature is significantly greater in the proximal region than in the distal region.
- Understanding tibial curvature is essential for accurate surgical planning and avoiding postoperative complications.
- This study presents a practical morphometric method for evaluating posterior tibial curvature on the sagittal plane.

Cite this article as: Sener H, Sonmez HK. Evaluating peripapillary choroidal vascularity index and peripapillary retinal nerve fiber layer thickness in patients with retrobulbar optic neuritis: A comparative study. *Ann Med Res*. 2025;32(5):210–216. doi: 10.5455/annalsmedres.2025.01.02.

ABSTRACT

Aim: This study aimed to determine whether the peripapillary choroidal vascular index (pCVI) can be used to diagnose and track retrobulbar optic neuritis (RBON) and to compare the clinical and electrophysiological characteristics between patients with RBON and controls.

Materials and Methods: The study involved 60 eyes, and evaluations included magnetic resonance imaging (MRI), optical coherence tomography (OCT), visual field (VF) testing, and pattern visual-evoked potential (VEP) testing.

Results: Twenty eyes with RBON, twenty fellow eyes, and twenty healthy control eyes were enrolled. Age, gender, and axial length were not significantly different between the groups. Best-corrected visual acuity (BCVA) was substantially lower in RBON eyes than in both fellow and control eyes ($p<0.0167$). The peripapillary choroidal vascular index (pCVI) was also significantly reduced in the RBON eyes compared with the control eyes ($p<0.001$). Although RBON eyes showed longer P100 latency ($p = 0.019$) and reduced temporal peripapillary retinal nerve fiber layer (pRNFL) thickness ($p = 0.045$), these differences did not reach statistical significance.

Conclusion: Our findings demonstrate a reduction in pCVI and visual acuity in RBON eyes compared with controls, suggesting a potential role of vascular dysfunction in the disease process. Although other structural and electrophysiological changes were observed, they did not remain statistically significant.

Keywords: Optic neuritis, Choroidal vascularity index, Retinal nerve fiber layer, Visual evoked potential, Visual field

Received: Jan 02, 2025 **Accepted:** Apr 21, 2025 **Available Online:** May 26, 2025

INTRODUCTION

Retrobulbar optic neuritis (RBON), an inflammatory demyelinating disease that the optic nerve, is commonly associated with multiple sclerosis (MS) and neuromyelitis optica [1,2]. This disorder affects the part of the optic nerve behind the eye, resulting in visual abnormalities, such as color vision, blurred vision, and visual field deficiency [3]. Ongoing advances in imaging technology have led to an unprecedented increase in the detailed visualization of ocular structures, with a particular focus on the choroidal vasculature [4]. The choroid, a critical supplier of blood to the outer retina, is increasingly recognized for its role in several ocular pathologies [5].

The peripapillary choroidal vascular index (pCVI), which quantifies choroidal vessel density around the optic nerve head (ONH), has emerged as a promising tool for assessing optic nerve health [6]. However, studies evaluating the potential of pCVI for the diagnosis and monitoring of RBON are lacking.

This study aimed to investigate clinical and electrophysiological characteristics in patients with RBON and compare them to controls. The study also evaluated visual field (VF) outcomes, visual-evoked potential (VEP) tests, and changes in the retinal nerve fiber layer (RNFL) and pCVI among patients with RBON. This approach would help enhance our understanding of the disease's impact on optic nerve health and the potential role of choroidal vasculature in RBON.

https://doi.org/10.5455/annalsmedres.2025.01.02

MATERIALS AND METHODS

All methods employed in this research involving human participants strictly followed the ethical norms of the Helsinki Declaration. The research protocol received approval from the Institutional Review for ethical scientific conduct (Erciyes University Local Ethics Committee, No:2023/39).

Study population

This study included patients who presented with acute vision loss and were subsequently diagnosed with RBON at our institution. Comparisons were conducted between the affected eye and the healthy fellow eye of each patient, as well as with a randomly selected eye of a healthy patient attending the clinic. We excluded patients with a history of other ophthalmologic or neurologic diseases that could potentially influence the optic nerve, individuals with a medical history of bilateral retrobulbar neuritis, papillitis, and ischemic optic neuropathy, and those with pre-existing conditions such as diabetes or hypertension. Pediatric patients were also not included in this research. In patients diagnosed with RBON, images were obtained at least 3 months after the acute attack.

Clinical examination

All patients underwent a thorough ophthalmologic examination upon presentation, which included a dilated funduscopic examination, intraocular pressure (IOP) measurement, slit-lamp examination, and best-corrected visual acuity (BCVA) assessment. Relative afferent pupillary deficit (RAPD) was noted, and any aberrant findings were recorded.

Optical Coherence Tomography (OCT)

An ONH radial circle scan pattern and 24 continuous radial B-scans were obtained using the Spectralis OCT Glaucoma Module software (version 1.9.17.0; Heidelberg Engineering). The structures are arranged according to the axis running from the fovea to the Bruch's Membrane Opening (BMO) center. Every location along a predefined-diameter (3.5 mm) circle in a comprehensive area, as well as in the six different sectors, was used to calculate the thickness of the RNFL in the circumpapillary region (Figure 1).

VF test

We used the Octopus 900 perimeter (Haag-Streit, Switzerland) to perform the VF tests on our study participants. The VF test uses the 30-2 white/white pattern. Each subject was comfortably seated, and the test was performed in a dimly lit room. The nontested eye was occluded, and patients were instructed to fixate on the central target throughout the test. False-positive and false-negative responses and fixation losses were carefully recorded during the test to assess the reliability of the test results. Mean deviation (MD) is a measure quantifying the overall reduction or defect in a patient's visual field (VF) relative to the normal visual field of individuals in their age group. sLV measures the degree of localized VF loss.

Pattern VEP test

The VEP recordings were performed using the Vision Monitor by Metrovision (MonPack, France). This study was performed following the recommended standard protocol by the International Society for Clinical Electrophysiology of Vision (ISCEV) [7]. A thorough explanation of the process was provided to each patient, and measures were taken to optimize their visual acuity. The active electrode was positioned on the visual cortex (Oz region as per the international 10-20 system), the reference electrode was positioned on the midfrontal head region (Fz region), and the ground electrode was placed on the mastoid.

We employed a reversed checkerboard pattern as the stimulus. The chosen field size was 15 minutes of visual arc. The contrast level was kept equal to or above 85%, with an average luminance of approximately 100 cd/m^2. The temporal frequency was set at 2 pattern reversals per second (1Hz). The patient was situated a meter away from the screen. The patients' pupils were nondilated under ambient room illumination. The participants were instructed to maintain steady fixation at the center of the stimulus field. Needle electrodes were used. The recording time window was set for 250 milliseconds, with at least 100 sweeps averaged for each response. Furthermore, the bandpass was set at 1-30 Hz.

We measured the implicit time and amplitude of the positive wave at approximately 100 ms (P100) and the negative wave at approximately 75 ms (N75). The P100 amplitude was measured from the N75 trough to the next peak, while the N75 amplitude was calculated from the baseline to the negative trough. The time between the beginning of light and the peak of the waves is known as the implicit time.

Magnetic Resonance Imaging (MRI), diagnosis, and treatment

Patients with RBON based on clinical examination were referred for neuroimaging. The MRI of the craniocervical and orbital region with gadolinium was performed to confirm the diagnosis. The diagnosis of RBON is based on a combination of clinical findings, such as sudden unilateral visual loss, the presence of RAPD and color vision loss, and a combination of test results of prolonged VEP implicit time and VF defects. Patients diagnosed with RBON were treated with a pulse prednisolone (Prednol-L, Gensenta, Turkey) therapy of 1g, administered over a period of 3–5 days.

OCT image processing procedure

The Choroidal Vascularity Index (CVI) was assessed using a 3.5-mm ONH radial circle scan, facilitated by the Spectralis Glaucoma Module software. Further information on the method used to measure CVI can be found in other sources [8–10]. Image binarization, the process of converting grayscale images to binary images, was performed using ImageJ software (version 1.47, available freely at https://imagej.net/Citing).

https://doi.org/10.5455/annalsmedres.2025.01.02

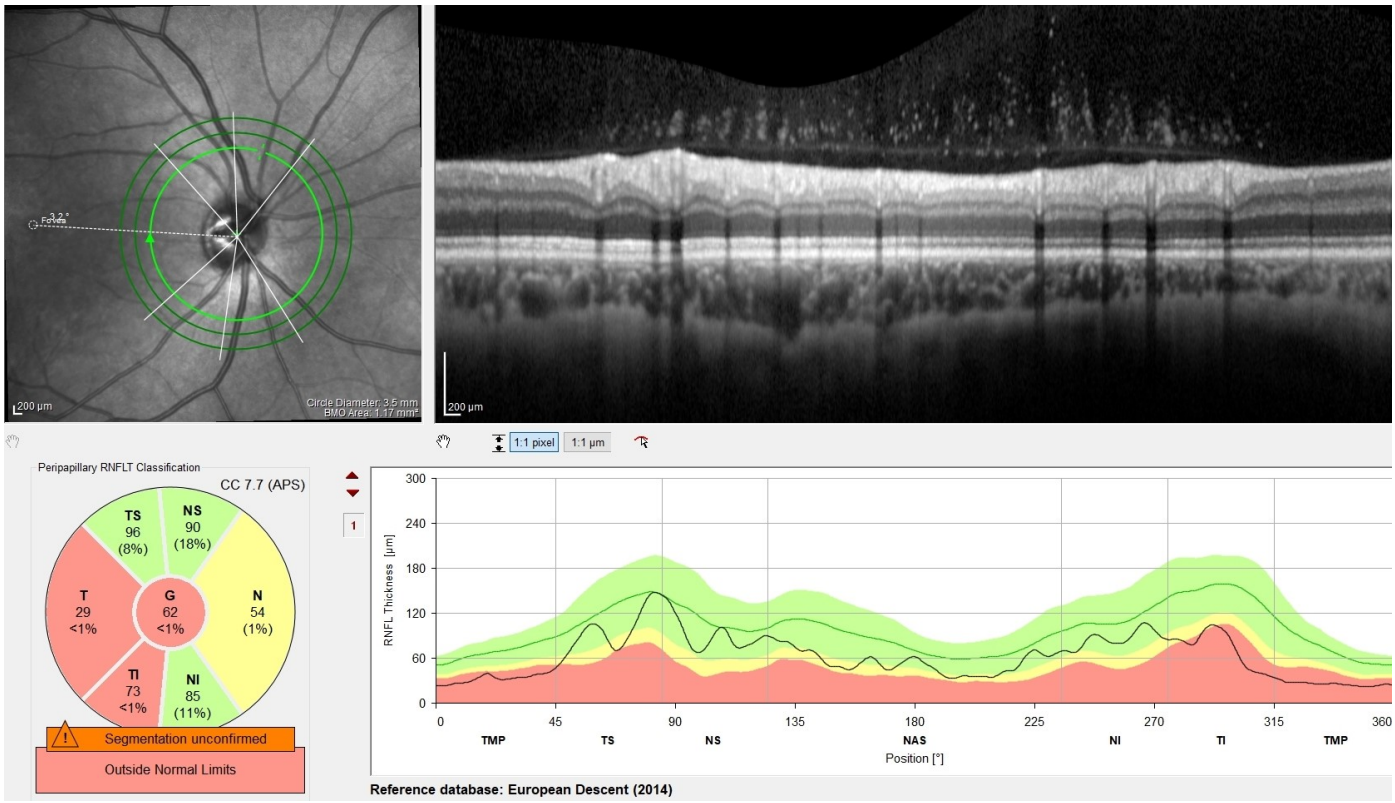

Figure 1. This figure shows the patient's SPECTRALIS Glaucoma Module scans with circumpapillary RNFL and optic disc imaging. The 3.5-mm RNFL scan results were obtained using the TSNIT profile and 6-sector analysis.

The area between the upper boundary of the light pixels at the Retinal Pigment Epithelium (RPE) and the lower boundary at the choroid-scleral junction was determined to be the choroidal area. The Total Choroidal Area (TCA), which is the area between the RPE and the choroid-scleral junction, was calculated after the picture color was changed to yellow so that the color threshold tool could detect dark pixels. The vascular region of dark pixels inside the choroid was identified as the Luminal Area (LA). Next, the LA was divided by the TCA to determine the pCVI (Figure 2).

Statistical analysis

All statistical analyses were performed using Statistical software Package for Social Sciences version 22 (SPSS version 22.0) (IBM Corp., Armonk, NY, USA). Shapiro-Wilk test was used as the test of normality. Homogeneity of variances was assessed using Levene's test. Based on these tests, statistical differences between groups were evaluated using the relevant parametric or nonparametric test. The Pearson chi-square test was used to compare nominal data.

Non-normally distributed data were subjected to the Wilcoxon signed-rank test. The Student's t-test was used for normally distributed data, whereas the Mann–Whitney U test was used for data that was not for independent groups. The results are displayed as mean ± standard deviation (SD) for normally distributed data and as median and interquartile range (IQR: 25^{th} to 75^{th} percentile) for nonnormally distributed data.

Comparisons among the three groups (RBON eyes, fellow eyes, and control eyes) were performed using paired or independent t-tests, as appropriate. To control for type I errors caused by multiple comparisons, Bonferroni correction was used. The significance threshold was adjusted to $\alpha = 0.05/3 \approx 0.0167$.

A post-hoc power analysis was conducted using G*Power software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) to assess whether the sample size was sufficient to detect differences in the peripapillary choroidal vascularity index (pCVI) among the three groups. The analysis was based on a one-way ANOVA (fixed effects, omnibus), with an alpha level of 0.05, three groups, and an effect size (Cohen's f) derived from the observed means and standard deviations. The resulting statistical power and Type II error probability (β) were calculated accordingly.

RESULTS

Twenty eyes with RBON, twenty buddy eyes, and twenty healthy control eyes comprised the total number of eyes enrolled. The patient and control groups did not differ significantly in terms of sex (p=0.185) or age [patient group: 41.0 (26.0-43.7, control group: 28.0 (30.0-32.0); p=0.056]. Eyes with RBON, other eyes, and controls had comparable axial lengths. However, compared with the controls and other eyes, eyes with RBON showed a markedly lower BCVA (Table 1). Nine members of the RBON group had relapsing-remitting multiple sclerosis.

https://doi.org/10.5455/annalsmedres.2025.01.02

Table 1. Demographic and clinical characteristics of patients.

Variables	RBON eye (n=20)	Fellow eye (n=20)	Control eye (n=20)	p1	p2	p3
Age (year)	41.0 (26.0-43.7)		28.0 (30.0-32.0)		0.056	
Sex (m/f)	5/15		9/11		0.185	
BCVA (decimal)	0.95 (0.62-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	**0.007***	**0.006***	0.289
Axial lenght (mm)	23.1±1.0	23.2±1.0	23.7±1.0	0.618	0.124	0.154

*BCVA: best-corrected visual acuity; p1: RBON eye v fellow eye; p2: RBON eye v control eye; p3: fellow eye v control eye, RBON: retrobulbar optic neuritis, *significant p value.*

Table 2. Electrophysiological tests results of patients with RBON.

Variables	RBON eye (n=20)	Fellow eye (n=20)	p
N75_IT (ms)	61.2 (38.0-77.3)	72.9 (45.5-78.4)	0.455
N75_A (mV)	1.3 (0.2-2.9)	0.5 (0.2-1.9)	0.130
P100_IT (ms)	115.3±13.5	104.6±9.3	0.019
P100_A (mV)	8.1±4.0	8.6±5.1	0.452
Visual Field (md)	6.1±4.	4.2±3.4	0.078
Visual Field (sLV)	6 4.9±2.1	4.1±1.8	0.051

*RBON: retrobulbar optic neuritis, *significant p value.*

Table 3. OCT test results of patients and controls.

Variables	RBON eye (n=20)	Fellow eye (n=20)	Control eye (n=20)	p1	p2	p3
pRNFL_T (µm)	59.8±18.8	64.9±15.7	69.6±9.3	0.154	0.045	0.259
pRNFL_IT (µm)	142.0±44.3	139.1±30.8	146.8±14.7	0.741	0.649	0.323
pRNFL_IN (µm)	107.1±25.8	103.3±21.7	106.0±18.4	0.434	0.878	0.625
pRNFL_N (µm)	79.1±19.6	75.5±22.1	84.5±14.2	0.348	0.330	0.135
pRNFL_SN (µm)	122.5±28.5	115.7±25.9	118.8±28.3	0.265	0.683	0.724
pRNFL_ST (µm)	119.1±33.7	118.6±25.7	132.7±23.0	0.928	0.145	0.323

*RBON: retrobulbar optic neuritis; RNFL: retinal nerve fibre layer; p1: RBON eye v fellow eye; p2: RBON eye v control eye; p3: fellow eye v control eye, *significant p value.*

Table 4. CVI results of patients and controls.

Variables	RBON eye (n=20)	Fellow eye (n=20)	Control eye (n=20)	p1	p2	p3
CVI (%)	67.9±2.3	68.3±1.3	69.8±3.3	0.323	0.042	0.070
TCA (mm^2)	4.1±1.2	4.0±0.9	2.3±0.5	0.469	**<0.001***	**<0.001***
LA (mm^2)	2.8±0.8	2.8±0.6	1.6±0.4	0.575	**<0.001***	**<0.001***
SA (mm^2)	1.3±0.5	1.3±0.3	0.7±0.2	0.338	**<0.001***	**<0.001***
LA/SA (%)	0.48±0.05	0.46±0.02	0.44±0.07	0.240	0.047	0.102

*CVI: choroidal vascularity index, TCA: total choroidal area, LA: luminal area, SA: stromal area, p1: RBON eye v fellow eye; p2: RBON eye v control eye; p3: fellow eye v control eye, *significant p value.*

The eyes with RBON and the other eyes were the only ones whose VEP and VF test results were compared. The amplitude of the P100 wave and the implicit timing and amplitude of the N75 wave did not significantly differ between the eyes with RBON and the other eyes. Although the eyes with RBON showed a longer implicit time for the P100 wave (p = 0.019), this difference did not reach statistical significance. There was no significant difference in visual field (VF) between eyes with RBON and control eyes (Table 2).

The RBON eye had a lower average peripapillary retinal nerve fiber layer thickness (pRNFL_T) than the control eye (59.8 µm vs. 69.6 µm), but the difference was not statistically significant (p = 0.045). The RBON, fellow, and control eyes did not differ significantly in average pRNFL thickness across different sectors (Table 3).

CVI of the eyes with RBON was significantly lower than that of the control eye (67.9% vs. 69.8%, p < 0.001); however, the difference between the RBON and fellow eyes (p = 0.042) did not reach statistical significance. TCA, LA, and SA of the eyes with RBON were significantly lower in comparison to the fel-

https://doi.org/10.5455/annalsmedres.2025.01.02

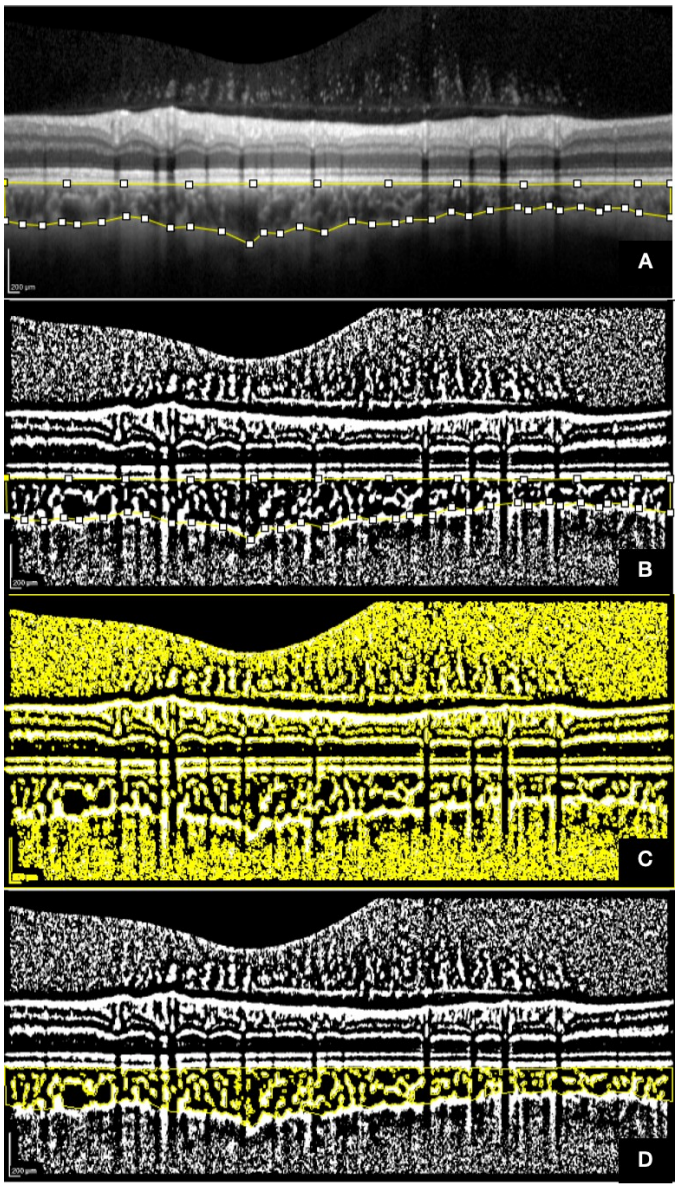

Figure 2. This sequence of images illustrates the process of image binarisation using ImageJ software. (A) The total peripapillary choroidal area was determined using the polygon tool in ImageJ software. (B) The image was then converted to an 8-bit image and autolocal thresholding was applied. (C) The Niblack method was selected to obtain a clear segmentation of the choroidal black and white areas. (D) Finally, the binarized image was converted back to an RGB image.

low normal eye (all p values < 0.001). The LA/SA ratio was lower in RBON eyes than in controls, but the difference was not statistically significant (Table 4).

A post-hoc power analysis was conducted to evaluate if the sample size was sufficient to detect group differences in pCVI. The mean pCVI values were 67.9% in RBON eyes, 68.3% in fellow eyes, and 69.8% in control eyes, with standard deviations of 2.3, 1.3, and 3.3, respectively. A one-way ANOVA was used to assess differences among the three groups. Based on these values, the calculated effect size (Cohen's f) was 0.44, indicating a moderate-to-large effect. With a sample size of 20 participants per group and a significance level (α) of 0.05, the probability of committing a Type II error (β) was approximately 0.155. Accordingly, the achieved statistical power was 84.5%, surpassing the conventional threshold of 80% required for adequate power. These findings suggest that the study was sufficiently powered to detect statistically significant differences in pCVI among groups, thereby reinforcing the robustness of the reported outcomes.

DISCUSSION

We aimed to elucidate the role of the choroidal vasculature in the pathophysiology of RBON by evaluating pRNFL thickness and pCVI in patients with RBON, fellow eyes, and control eyes. Our results showed a decrease in both temporal pRNFL thickness and pCVI in eyes with RBON compared with fellow and control eyes; however, these differences did not reach statistical significance. Although this trend may point to possible structural and vascular involvement in RBON, the lack of statistical significance limits the strength of this interpretation. The observed reduction in temporal pRNFL thickness may indicate the potential involvement of the papillomacular bundle. Nonetheless, the significant decline in BCVA in RBON eyes supports a functional impact on visual acuity, possibly reflecting a combination of inflammatory and microvascular processes.

The function of peripapillary choroidal microvasculature dropout (MvD) in individuals with optic neuritis was examined in a recent study by Lee et al. [11]. According to their research, MvD was more prevalent in the temporal quadrant and was detected in 41.7% of eyes with optic neuritis. Our findings of weakening of the temporal pRNFL in eyes with RBON are comparable to this one. In his study, during the 6-month follow-up, a smaller ganglion cell inner plexiform (GCIP) layer thickness was strongly correlated with the occurrence of MvD. MvD-affected eyes also exhibited reduced temporal quadrant peripapillary retinal vascular density. These results imply that MvD is linked to structural disturbance of the macular GCIP in patients with optic neuritis, which may result in poor visual prognosis. Notably, our results and those of Lee et al. [11] demonstrate how crucial the choroidal vasculature in the pathophysiology of these conditions.

According to a different study by Lee et al. [12], glaucoma and compressive optic neuropathy share MvD, but they present and have different characteristics. In particular, MvD was found in the temporal inferior and superior sectors of the temporal peripapillary sector in glaucoma and compressive optic neuropathy. In addition, MvD development in compressive optic neuropathy was linked to a notable decrease in RNFL thickness and retinal vascular density, which were not observed in glaucoma.

Balci et al. [13] reported a mean macular CVI of 59.6% in affected eyes compared with 61.7% in unaffected eyes in patients with MS who had an optic neuritis attack, suggesting that their attacks may lead to choroidal vascular damage. However, it is important to note that Balci et al found a reduction

https://doi.org/10.5455/annalsmedres.2025.01.02

in macular CVI in affected eyes compared with unaffected fellow eyes, but not in healthy controls.

The fact that MS is commonly associated with optic nerve inflammation [14]. The condition is typically characterized by brain lesions characterized by $CD8^+$ T-cell–mediated inflammatory demyelination [15]. Perivascular accumulations of activated complement proteins and immunoglobulins are typically present within these affected lesions [16] In addition, perivascular infiltration by myelin oligodendrocyte glycoprotein-laden macrophages and $CD4^+$ T cells has also been observed in these lesions [16,17] Numerous OCT-Angio studies have shown reduced macular superficial capillary plexus vessel density in MS patients, suggesting that this may be due to reduced oxygen and metabolite demand secondary to neuroaxonal degeneration and pRFNL and GCIP atrophy [18]. However, other investigators have suggested that MS- or ON-induced inflammation has a direct effect on endothelial dysfunction [19]. Interestingly, previous studies have shown that changes in retinal vascular density share the same characteristics as reduced blood flow in cerebral MS lesions [20,21] This overlap highlights the potential importance of our findings regarding the choroidal vasculature in RBON, as it suggests that the vascular changes we observed may reflect global vascular changes.

One of our study's weaknesses is the small number of patients, which could limit the broad applicability of our findings. Larger cohort studies are necessary in the future to confirm and broaden our findings. In addition, our inability to perform a sectoral analysis of the pCVI is a notable limitation. Incorporating a pretreatment and posttreatment analysis of pCVI could provide valuable insight into the treatment effect on choroidal changes. Future research should consider a sectoral approach to pCVI to identify sector-specific variations indicative of RBON. These steps are critical for advancing our understanding of RBON and may open avenues for novel therapeutic strategies by more thoroughly exploring the vascular aspects of this condition.

CONCLUSION

In conclusion, our study demonstrated a reduction in pCVI and visual acuity in eyes affected by RBON compared with control eyes, supporting the potential role of vascular dysfunction in the disease process. Although reductions in temporal pRNFL thickness and fellow-eye pCVI were observed, these differences did not reach statistical significance. These findings suggest that choroidal vascular alterations, alongside inflammatory mechanisms, may contribute to the pathophysiology of RBON and warrant further investigation in larger cohorts.

Ethics Committee Approval: The research protocol received approval from the Erciyes University Local Ethics Committee (No:2023/39).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: H.S.; Design: H.S.; Data Collection and/or Processing: H.S.; Analysis and/or Interpretation: H.K.S.; Literature Review: H.K.S.; Writing: H.S.; Critical Review: H.K.S.

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

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

REFERENCES

1. Beck RW. The optic neuritis treatment trial: three-year follow-up results. *Arch Ophthalmol.* 1995;113(2):136-137. doi: 10.1001/archopht.1995.01100020014004.
2. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology.* 2015;85(2):177-189. doi: 10.1212/wnl.0000000000001729.
3. Balcer LJ. Clinical practice. Optic neuritis. *N Engl J Med.* 2006;354(12):1273-1280. doi: 10.1056/NEJMcp053247.
4. Imamura Y, Fujiwara T, Margolis RON, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. *Retina.* 2009;29(10):1469-1473. doi: 10.1097/iae.0b013e3181be0a83.
5. Nickla DL, Wallman J. The multifunctional choroid. *Prog Retin Eye Res.* 2010;29(2):144-168. doi: 10.1016/j.preteyeres.2009.12.002.
6. Park JW, Suh MH, Agrawal R, Khandelwal N. Peripapillary choroidal vascularity index in glaucoma—A comparison between spectral-domain OCT and OCT angiography. *Invest Ophthalmol Vis Sci.* 2018;59(8):3694-3701. doi: 10.1167/iovs.18-24315.
7. Odom JV, Bach M, Brigell M, et al. ISCEV standard for clinical visual evoked potentials:(2016 update). *Doc Ophthalmol.* 2016;133:1-9. doi: 10.1007/s10633-016-9553-y.
8. Agrawal R, Gupta P, Tan KA, Cheung CMG, Wong TY, Cheng CY. Choroidal vascularity index as a measure of vascular status of the choroid: measurements in healthy eyes from a population-based study. *Sci Rep.* 2016;6(1):21090. doi: 10.1038/srep21090.
9. Agrawal R, Salman M, Tan KA, et al. Choroidal vascularity index (CVI)-a novel optical coherence tomography parameter for monitoring patients with panuveitis? *PLoS One.* 2016;11(1):e0146344. doi: 10.1371/journal.pone.0146344.
10. Suh MH, Park JW, Khandelwal N, Agrawal R. Peripapillary choroidal vascularity index and microstructure of parapapillary atrophy. *Invest Ophthalmol Vis Sci.* 2019;60(12):3768-3775. doi: 10.1167/iovs.18-26286.
11. Lee JS, Park S, Kim SS, et al. Peripapillary choroidal microvasculature dropout is associated with poor prognosis in optic neuritis. *PLoS One.* 2023;18(4):e0285017. doi: 10.1371/journal.pone.0285017.
12. Lee EJ, Kim JA, Kim TW, et al. Glaucoma-like parapapillary choroidal microvasculature dropout in patients with compressive optic neuropathy. *Ophthalmology.* 2020;127(12):1652-1662. doi: 10.1016/j.ophtha.2020.06.001.
13. Balci S, Ozcelik Kose A, Yenerel NM. The effect of optic neuritis attacks on choroidal vascularity index in patients with multiple sclerosis. *Graefe's Arch Clin Exp Ophthalmol.* 2021;259:2413-2424. doi: 10.1007/s00417-021-05143-x.
14. Toosy AT, Mason DF, Miller DH. Optic neuritis. *Lancet Neurol.* 2014;13(1):83-99. doi: 10.1016/s1474-4422(13)70259-x.

https://doi.org/10.5455/annalsmedres.2025.01.02

15. Machado-Santos J, Saji E, Tröscher AR, et al. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident $CD8^+$ T lymphocytes and B cells. *Brain.* 2018;141(7):2066-2082. doi: 10.1093/brain/awy151.
16. Takai Y, Misu T, Kaneko K, et al. Myelin oligodendrocyte glycoprotein antibody-associated disease: an immunopathological study. *Brain.* 2020;143(5):1431-1446. doi: 10.1093/brain/awaa102.
17. Marignier R, Hacohen Y, Cobo-Calvo A, et al. Myelin-oligodendrocyte glycoprotein antibody-associated disease. *Lancet Neurol.* 2021;20(9):762-772. doi: 10.1016/s1474-4422(21)00218-0.
18. Mohammadi S, Gouravani M, Salehi MA, et al. Optical coherence tomography angiography measurements in multiple sclerosis: a systematic review and meta-analysis. *J Neuroinflammation.* 2023;20(1):85. doi: 10.1186/s12974-023-02763-4.
19. Murphy OC, Kwakyi O, Iftikhar M, et al. Alterations in the retinal vasculature occur in multiple sclerosis and exhibit novel correlations with disability and visual function measures. *Mult Scler J.* 2020;26(7):815-828. doi: 10.1177/1352458519845116.
20. Paling D, Thade Petersen E, Tozer DJ, et al. Cerebral arterial bolus arrival time is prolonged in multiple sclerosis and associated with disability. *J Cereb Blood Flow Metab.* 2014;34(1):34-42. doi: 10.1038/jcbfm.2013.161.
21. Inglese M, Adhya S, Johnson G, et al. Perfusion magnetic resonance imaging correlates of neuropsychological impairment in multiple sclerosis. *J Cereb Blood Flow Metab*. 2008;28(1):164-171. doi: 10.1038/sj.jcbfm.9600504.

https://doi.org/10.5455/annalsmedres.2025.01.02

Ann Med Res

Current issue list available at Ann Med Res

Annals of Medical Research

journal page: annalsmedres.org

Types of the maxillary labial frenulum and median diastema in children: A cross-sectional study

Zekiye Seyma Gumusboga [a,*], Seyda Merve Yabas [a]

[a]Inonu University, Faculty of Dentistry, Department of Pedodontics, Malatya, Türkiye
*Corresponding author: seymasizer@gmail.com (Zekiye Seyma Gumusboga)

MAIN POINTS

- The most common frenulum type was found to be gingival frenulum, while the least common was papillary penetrating frenulum.
- There is a relationship between frenulum type and diastema.
- Papillary penetrating frenulum can cause median diastema.

Cite this article as: Gumusboga ZS, Yabas SM. Types of the maxillary labial frenulum and median diastema in children: A cross-sectional study . *Ann Med Res*. 2025;32(5):217–221. doi: 10.5455/annalsmedres.2025.01.09.

ABSTRACT

Aim: The aim of this study is to determine the frequency of different types of maxillary labial frenulum in children aged 4-13 years and whether they have an effect on median diastema.

Materials and Methods: This study is a cross-sectional study conducted on 723 children aged 4-13 years who applied to the Department of Pedodontics, Faculty of Dentistry, Inonu University for examination. The examination of the children participating in the study was performed by sitting them upright under normal light. The patient's frenulum type was determined by performing the blanch test. The diastema between the maxillary central teeth was measured with an orthodontic caliper and was recorded.

Results: The data were analyzed descriptively and analytically. 343 boys and 380 girls were examined in this study. The most common maxillary labial frenulum type in the examined children was found to be the gingival frenulum type (57%), and the least common maxillary labial frenulum type was the papillary penetrating frenulum type (2%). When we looked at the amount of diastema in our study, the median diastema was mostly between 0-2 mm in the primary dentition, while the median diastema was mostly not seen in the mixed and permanent dentition.

Conclusion: As a result, it was seen that there was a significant relationship between frenulum type and median diastema, but there was no significant relationship between gender and frenulum type.

Keywords: Median diastema, Maxillary labial frenulum, Children

Received: Jan 07, 2025 **Accepted:** Apr 28, 2025 **Available Online:** May 26, 2025

INTRODUCTION

The maxillary labial frenulum is a thin strip or fold of mucous tissue extending from the middle of the maxillary gum to the middle of the upper lip. The height and location vary from person to person [1]. During early childhood, it is small, wide, and positioned more cervical, but undergoes subsequent changes with the eruption of the deciduous incisors, development of the maxillary sinus, and increase in the alveolar vertical dimension [2, 3]. Alveolar crest height increases with new bone apposition during deciduous dentition, notwithstanding the consistent positioning of the frenulum. While the upper central incisors commonly erupt with a diastema in the mixed dentition period, the later pressure exerted by the lateral incisors and canines usually diminishes this gap, facilitating closer alignment of the central incisors [1].

The maxillary labial frenulum, despite being associated with multiple complications, most notably causes a median diastema. This diastema presents challenges for orthodontic treatment, potentially leading to relapse. Moreover, it has been shown to contribute to caries in breastfed infants and may impair future oral hygiene effectiveness [4, 5]. Dysfunction of the frenulum can further result in gingival recession, aberrant tooth positioning, papillary loss, and an elevated caries risk due to poor oral hygiene. This condition can also exacerbate periodontal issues and contribute to psychological disturbances [3, 6, 7].

Frenulum are classified according to their anatomical location [4, 5]. In the frenulum 1974, Placek et al. classified the frenulum into four types according to its location: mucosal, gingival, papillary, and papillary penetrating [9]. This classification gained acceptance among periodontists, orthodontists, and pediatric dentists and continues to be utilized [2, 3, 10]. The mucosal and gingival frenulum types are considered within the normal range, whereas the papillary and papillary pene-

trating types are deemed pathological. Notably, pathological frenula are implicated in greater papilla loss, gingival problems, diastema development, and challenges in maintaining interdental hygiene [11].

Existing literature includes several studies on the frequency of maxillary labial frenula in adults, adolescents, and children, employing diverse classification systems. However, the distribution of maxillary frenulum types and their association with median diastema in children specifically within the Malatya region has not been explored. Consequently, this cross-sectional epidemiological study was designed to ascertain the prevalence of different labial frenulum types and their relationship to median diastema in children across various dentition stages living in Malatya province. The study's null hypothesis (H0) posited no association between labial frenulum types and median diastema spacing, while the alternative hypothesis (H1) suggested a relationship between these variables.

MATERIALS AND METHODS

This observational, cross-sectional epidemiological study was conducted at the Pediatric Dentistry Clinic of the Faculty of Dentistry at Inonu University in Malatya, Türkiye. The study received approval from the Clinical Research Ethics Committee of Malatya İnönü University (2024/66), and written informed consent was obtained from the legal guardians of all participating patients. Between May 20, 2024, and October 20, 2024, 723 systemically healthy children aged 4-13 years who presented to the clinic for examination were included.

Children exhibiting orofacial anomalies (including cleft lip and palate), a history of maxillary labial surgery, use of medications causing gingival overgrowth, congenital upper lip and oral muscle deformities, or absence of maxillary central incisors were excluded. Additionally, children with interproximal caries or fillings in the upper central incisors, those with size or shape alterations of the upper central incisors, a history of corrective orthodontic treatment, excessive rotation of the upper central incisors, or the presence of supernumerary teeth (mesiodens), odontomas, or other conditions in the upper central region that could cause diastema were also excluded.

The required sample size was calculated using G Power 3.1.9 software. Based on a prior study by Seraj et al. [12], which reported a low effect size (0.010–0.20) when examining maxillary labial frenulum types and median diastema in 3–6-year-old children, an a priori power analysis with an assumed effect size of 0.20, a type I error rate (α) of 0.05, and a desired power ($1 - \beta$) of 0.99 indicated a minimum sample size of 542. Of the 2,454 patients who visited the pedodontics clinic between May 20 and October 20, 2024, 840 were examined, and 117 were excluded due to not meeting the inclusion criteria, resulting in a final sample of 723 participants. Clinical examinations were performed under unit light by two experienced investigators. Frenulum classification followed Placek et al.'s method [9], involving stretching the upper lip with the index and thumb of both hands. A frenulum attachment above the mucogingival junction was classified as mucosal; attachment in the attached gingiva apical to the papilla base was gingival; attachment coronal to the papilla base but not palatally was papillary; and a frenulum extending palatally into the papilla was papillary penetrating. In cases of median diastema, the spacing was measured in millimeters using an orthodontic caliper. Patient age, gender, and dentition stage were also recorded. Diastema size was categorized as 0 mm (absence), 0-2 mm (normal), and ≥2 mm (pathological) [2].

Statistical analysis

All data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM, Armonk, NY, USA). Descriptive statistics included percentages for gender, age, and frenulum type. The relationships between variables were examined using appropriate statistical tests. The Pearson Chi-square test was used to assess the association between upper lip frenulum type, gender, and dentition period. The Fisher-Freeman-Halton Exact Test was used to analyze the relationship between median diastema and dentition period, as well as frenulum types. The significance level for all analyses was set at $p<0.05$.

RESULTS

A total of 723 children participated in this study, comprising 343 males and 380 females, with an age range of 4 to 13 years (mean age ± standard deviation: 9.4 ± 2.3 years). The prevalence of maxillary labial frenulum types is illustrated in Figure 1. The most frequently observed type was gingival (57%), followed by mucosal (37%), papillary (4%), and papillary penetrating (2%). No statistically significant correlation was found between maxillary frenulum type and sex (p = 0.063) (Table 1).

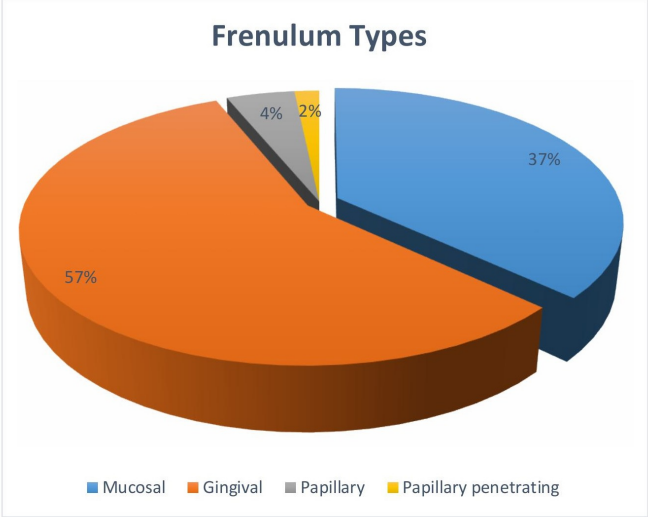

Figure 1. Distribution of maxillary labial frenulum types.

https://doi.org/10.5455/annalsmedres.2025.01.09

Table 1. The association between maxillary labial frenulum types and gender.

Gender	Frenulum types					P value
	Mucosal n (%)	Gingival n (%)	Papillary n (%)	Papillary penetrating n (%)	Total n (%)	
Girl	125 (46.8)	226 (55)	22 (66.7)	7 (58.3)	380 (52.6)	0.063
Boy	142 (53.2)	185 (45)	11 (33.3)	5 (41.7)	343 (47.4)	
Total	267 (36.9)	411 (56.8)	33 (4.6)	12 (1.7)	723 (100)	

Pearson Chi square test. Shows statistically significant differences at p<0.05.

Table 2. The association between maxillary labial frenulum types and dentition period.

Frenulum types	Dentition period				P value
	Deciduous dentition n (%)	Mixed dentition n (%)	Permanent dentition n (%)	Total n (%)	
Mucosal	9 (17.6)	159 (33.5)	99 (50)	267 (36.9)	0.00
Gingival	36 (70.6)	281(59.3)	94 (47.5)	411 (56.8)	
Papillary	4 (7.8)	25 (5.3)	4 (2)	33 (4.6)	
Papillary penetrating	2 (3.9)	9 (1.9)	1 (0.5)	12 (1.7)	
Total	51 (7.1)	474 (65.6)	198 (27.4)	723 (100)	

Pearson Chi square test. Shows statistically significant differences at p<0.05.

Table 3. The association between median diastema and dentition period.

Median diastema	Dentition period				P value
	Deciduous dentition n (%)	Mixed dentition n (%)	Permanent dentition n (%)	Total n (%)	
There is no diastema	16 (31.4)	241 (50.8)	169 (85.4)	426 (58.9)	0.00
0-2 mm between diastema	28 (54.9)	119 (25.1)	23 (11.6)	170 (23.5)	
2 mm and above diastema	7 (13.7)	114 (24.1)	6 (3)	127 (17.6)	
Total	51 (7.1)	474 (65.6)	198 (27.4)	723 (100)	

Fisher's Freman Halton Exact Test. Shows statistically significant differences at p<0.05.

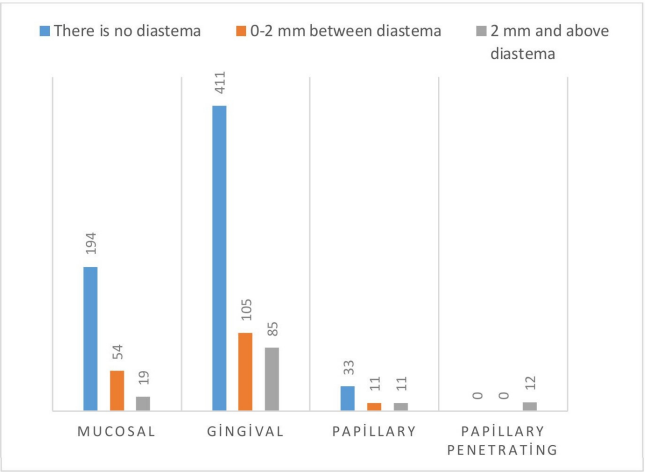

Figure 2. Relationship between maxillary labial frenulum types and maxillary median diastema.

Table 2 presents the relationship between maxillary frenulum type and dentition period, revealing a statistically significant correlation (p<0.001). The association between maxillary labial frenulum type and diastema spacing is depicted in Figure 2, which also demonstrates a statistically significant relationship (p<0.001). The relationship between diastema spacing and dentition period is detailed in Table 3.

DISCUSSION

This study investigated the prevalence of maxillary labial frenulum types, median diastema spacing, and their relationship in 723 children aged 4-13 years in Malatya, Türkiye. Our findings indicate that the most common frenulum type was gingival (57%), and the least common was papillary penetrating (2%). These prevalence rates are generally consistent with studies conducted in other Turkish regions, such as İzmir (Kılınç et al. [13]), Bolu (Güler et al. [10]), and Istanbul (Taran et al. [14]), which also reported gingival frenulum as the most prevalent (43.7%, 43%, and 45.8%, respectively) and papillary penetrating as the least prevalent (7.2%, 11%, and 13.1%, respectively). Boutsi and Tatakis [4] in their study found a similar high prevalence of gingival frenulum (41.6%), but a higher prevalence of papillary frenulum (22.1%) compared to our findings. Placek et al. [9], whose classification we adopted, reported mucosal frenulum as the most common (46.5%), followed by gingival (34.3%). These variations

https://doi.org/10.5455/annalsmedres.2025.01.09

in prevalence across studies might be attributed to differences in ethnic origin or geographical location.

Güler et al. [10] observed a higher prevalence of gingival frenulum during the deciduous and mixed dentition periods. Our study aligns with this, finding gingival frenulum most common in these stages, while mucosal frenulum was more prevalent in the permanent dentition. Clinically, mucosal and gingival frenula are considered normal, whereas papillary and papillary penetrating types are pathological and associated with papilla loss, gingival problems, diastema, and difficulties in interdental cleaning [11].

In our study, no statistically significant relationship was found between frenulum type and sex or age ($p = 0.063$), which is consistent with the findings of Kılınç et al. [13] and Placek et al. [9]. While Güler et al. [10] and Kılınç et al. [13] did not find a significant association between frenulum type and dentition period, our study revealed a statistically significant relationship ($p<0.001$).

A diastema is defined as a gap exceeding 0.5 mm between teeth [9], and while common in deciduous and mixed dentition, these gaps often close with the eruption of canines [15]. A persistent median diastema can be attributed to the maxillary labial frenulum attachment [16]. In such cases, clinical and radiographic evaluation is crucial. For frenulum-induced diastema in pediatric patients, treatment aims to close the gap and eliminate the causative frenulum [17]. Careful examination of the frenulum is essential in pediatric dental assessments. While a diastema during the "ugly duckling stage" of mixed dentition (typically up to 2 mm) is often physiological, gaps wider than 2 mm warrant consideration of the etiology, as spontaneous closure is less likely, potentially requiring orthodontic intervention [2].

In our study, we examined frenulum types and measured median diastema spacing. Diastema gaps were most frequently between 0 and 2 mm in the primary dentition and often absent in the mixed and permanent dentition. Notably, all children with the papillary penetrating frenulum type had a median diastema of 2 mm or more. We found a statistically significant relationship between frenulum type and diastema gap ($p<0.001$), which is consistent with the findings of , Seraj et al. otherwise ($p=0.014$) and Sękowska et al. ($p<0.05$), but contrasts with the findings of Sagar et al. [12,16, 17]. These discrepancies may arise from variations in frenulum classifications and the age ranges of the studied populations. We opted for Placek et al.'s classification due to its ease of use for periodontists, orthodontists, and pediatric dentists.

Clinicians should utilize the blanch test to aid in the visual detection of abnormal frenula [14]. For patients with frenulum-related concerns, monitoring until around 10 years of age is advisable, at which point frenectomy (surgical blade or laser) can be considered. In the absence of issues, regular follow-up is recommended [18].

A limitation of this study is its focus on a single city in eastern Türkiye. Future research should encompass a broader geographical range to provide a more comprehensive understanding of the relationship between frenulum type and diastema spacing in Turkish children across different regions.

CONCLUSION

In conclusion, while prior research has documented frenulum prevalence in various populations, this study identified gingival frenulum as the most common and papillary penetrating as the least common type in our Malatya cohort. Importantly, we found a significant association between frenulum type and median diastema. Therefore, meticulous frenulum examination by dentists, particularly pediatric dentists, is crucial. Patients should be educated about frenula potentially contributing to diastema. A key implication of this study is the need for timely and accurate frenulum assessment by orthodontists and pediatric dentists, facilitating collaborative intervention in cases of diastema caused by frenulum morphology.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Malatya İnönü University (2024/66).

Informed Consent: Written informed consent was obtained from the legal guardians of all participating patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: Z.S.G.; Design: Z.S.G.; Supervision: Z.S.G.; Materials: Z.S.G.; Data Collection and/or Processing: S.M.Y.; Analysis and/or Interpretation: S.M.Y.; Literature Review: Z.S.G.; Writing: S.M.Y.; Critical Review: S.M.Y.

Conflict of Interest: The authors declare no competing interests.

Financial Disclosure: No financial support was obtained for this study.

REFERENCES

1. Miotti, A. et al., Histologic characteristics of the upper labial frenum in individuals with middle interincisor diastema. *Mondo Odontostomatol.* 1979. 21(1):22-25.
2. Abu-Hussein, M. and North Watted, Maxillary midline diastema–Etiology and orthodontic treatment-clinical review. *IOSR J Dent Med Sci,* 2016. 15(6):116-30. doi: 10.9790/0853-150602116130.
3. Anubha, North et al. Frenectomy combined with a laterally displaced pedicle graft. *Indian J Dent Sci,* 2010. 2(2):47-51.
4. Boutsi, E.A. and D.N. Tatakis, Maxillary labial frenum attachment in children. *Int J Paediatr Dent.* 2011. 21(4):284-288. doi: 10.1111/j.1365-263X.2011.01121.x.
5. Broadbent, B.H.: 'The face of the normal child. *Angle Orthod.* 1937. 7(4):183-208.
6. Delli, K. et al. Facts and myths regarding the maxillary midline frenum and its treatment: a systematic review of the literature. *Quintessence Int.* 2013. 44(2):177-87. doi: 10.3290/j.qi.a28925.
7. Edwards, J.G., The diastema, the frenum, the frenectomy: a clinical study. *Am J Orthod.* 1977. 71(5):489-508. doi: 10.1016/0002-9416(77)90001-x.

https://doi.org/10.5455/annalsmedres.2025.01.09

8. Sewerin I. Prevalence of variations and anomalies of the upper labial frenum. *Acta Odontol Scand.* 1971. 29(4):487-496. doi: 10.3109/00016357109026535.
9. Mirko, P., South Miroslav, and M.J.J.o.p. Lubor, Significance of the labial frenum attachment in periodontal disease in man. Part 1. Classification and epidemiology of the labial frenum attachment. *J Periodontol,* 1974. 45(12):891-894. doi: 10.1902/jop.1974.45.12.891
10. Guler, D., Ş. Güler, and U. Öğütücü, Bolu ve Çevresinde Yaşayan Çocuklarda Labial Frenulum Tipleri ve Gingival Sağlığa Etkileri. *Anadolu Kliniği Tip Bilimleri Dergisi.* 2020. 25(2):108-111. doi: 10.21673/anadoluklin.598512.
11. Kotlow, L.A., The influence of the maxillary frenum on the development and pattern of dental caries on anterior teeth in breastfeeding infants: prevention, diagnosis, and treatment. *J Hum Lact.* 2010. 26(3):304-308. doi: 10.1177/0890334410362520.
12. Seraj, B. et al. Studying maxillary labial frenulum types and their effect on median diastema in 3–6-year-old Children in Tehran Kindergartens. *World J Dent,* 2019. 10(2):93-97. doi 10.5005/jp-journals-10015-1611.
13. Kılınç, G. et al., Çocuklarda Üst Çene Labial Frenulumun Klinik ve Diş Çürüğü Açısından Değerlendirilmesi. *Turkiye Klinikleri Journal of Dental Sciences,* 2014. 20(1).
14. Taran, P.K., et al. Evaluation of the Relationship Between Maxillary Labial Frenulum Attachment Types, Periodontal Health, and Dental Caries in Preschool Children. *Bezmialem Science.* 2023. 11(1):73-78. doi: 10.14235/bas.galenos.2022.20082.
15. Mohan, R., et al. Proposed classification of medial maxillary labial frenum based on morphology. *Dental Hypotheses.* 2014. 5(1):16-20. doi: 10.4103/2155-8213.128108.
16. Sagar, South, J. Heraldsherlin, and South Moses, Morphological variation of abnormal maxillary labial frenum in South Indian population. *Int. J. Pharm. Sci. Res.* 2016. 7(5):2142. doi: 10.13040/IJPSR.0975-8232.7(5).2142-46.
17. Sękowska, A. and R. Chałas, Diastema size and type of upper lip midline frenulum attachment. *Folia Morphol (Warsz).* 2017. 76(3):501-505. doi: 10.5603/FM.a2016.0079.
18. Thahir, H. et al. Management of maxillary labial frenum and comparison between conventional techniques and incision-below the-clamp technique: case report. *J Dentomaxillofac Sci*, 2018. 3(1):61-6. doi: 10.15562/jdmfs.v3i1.634.

https://doi.org/10.5455/annalsmedres.2025.01.09

Ann Med Res

Current issue list available at Ann Med Res

Annals of Medical Research

journal page: annalsmedres.org

A surprising diagnosis in a patient presenting with urticaria and uncontrolled asthma symptoms: A rare case of pleomorphic adenoma in the trachea

Selma Yesilkaya [a,*], Savas Gegin [b], Necmiye Gul Temel [c], Selcuk Gurz [d]

[a]Samsun Education and Research Hospital, Department of Chest Disease, Division of Immunology and Allergy, Samsun, Türkiye
[b]Samsun Education and Research Hospital, Clinic of Chest Diseases, Samsun, Türkiye
[c]Samsun University, Faculty of Medicine, Department of Thoracic Surgery, Samsun, Türkiye
[d]Ondokuz Mayıs University, Faculty of Medicine, Department of Thoracic Surgery, Samsun, Türkiye
*Corresponding author: selmayesilkaya@icloud.com (Selma Yesilkaya)

Cite this article as: Yesilkaya S, Gegin S, Temel NG, Gurz S. A surprising diagnosis in a patient presenting with urticaria and uncontrolled asthma symptoms: A rare case of pleomorphic adenoma in the trachea. *Ann Med Res*. 2025;32(5):222–225. doi: 10.5455/annalsmedres.2025.04.077.

ABSTRACT

Pleomorphic adenomas are the most common benign tumors of the salivary glands. Although they frequently occur in the parotid gland, they are rarely observed in the trachea. Diagnosis can be delayed because the symptoms may mimic those of asthma. In this case report, we present a case of pleomorphic adenoma in the trachea in a patient who had been experiencing intermittent urticaria for 2 years and had uncontrolled respiratory symptoms for the last 2 months despite clinical asthma treatment. This study aimed to raise awareness among clinicians about differential diagnoses by highlighting the absence of asthma and urticaria symptoms following tracheal lesion removal by thoracic surgery.

Keywords: Asthma, Urticaria, Pleomorphic adenoma, Trachea, Fixed obstruction
Received: Apr 07, 2025 **Accepted:** May 12, 2025 **Available Online:** May 26, 2025

INTRODUCTION

Urticaria and asthma are commonly encountered conditions in daily clinical practice. However, there are cases in which the symptoms of these two diseases may indicate rarer and more serious pathologies, necessitating careful differential diagnosis. Pleomorphic adenomas (PA) are benign tumors that typically arise in the salivary glands, albeit rarely observed in the trachea [1], and they may cause symptoms that might resemble those of asthma. The present case describes such a case of PA and is presented to create awareness regarding the possibility of underlying serious pathologies that can manifest with respiratory symptoms and chronic urticaria, even though it is a rare occurrence.

CASE REPORT

A 28-year-old female presented to our outpatient clinic of Immunology and Allergy Diseases with complaints of urticaria that had been ongoing for 2 years but had worsened in the last 2 months. She had been receiving asthma treatment for 2 years. The physical examination showed that there was stridor and wheezing. There were no signs of urticaria or angioedema during the physical examination.

The patient underwent a detailed evaluation of the etiology of urticaria. Considering the reported history of uncontrolled asthma despite treatment with high-dose salmeterol-fluticasone and montelukast, high-resolution computed tomography (HRCT) of the chest was performed. HRCT revealed a suspicious lesion in the trachea (Figure 1). Pulmonary function tests showed fixed obstruction in the flow-volume curve (Figure 2). The patient was referred to an otolaryngologist for endoscopic evaluation, which revealed no pathology. A bronchoscopy was then performed, revealing a mass lesion at the level of the second cartilage ring, obstructing 80% of the tracheal lumen (Figure 3). The tracheal lesion was excised via thoracic surgery using rigid bronchoscopy (Figure 4). The pathology report identified the lesion as PA. After the lesion was removed, the fixed upper airway obstruction observed in the flow-volume curve improved (Figure 5). A signed consent form was obtained from the patient on 28/06/2024.

DISCUSSION

Urticaria is characterized by hyperemic, itchy, eczematous papules or plaques on the surface of the skin and is classified

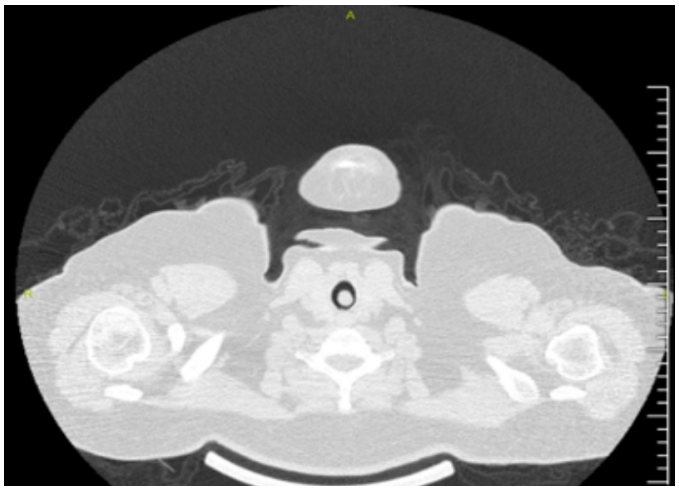

Figure 1. Appearance of a lesion occupying 80% of the tracheal lumen on high-resolution computed tomography.

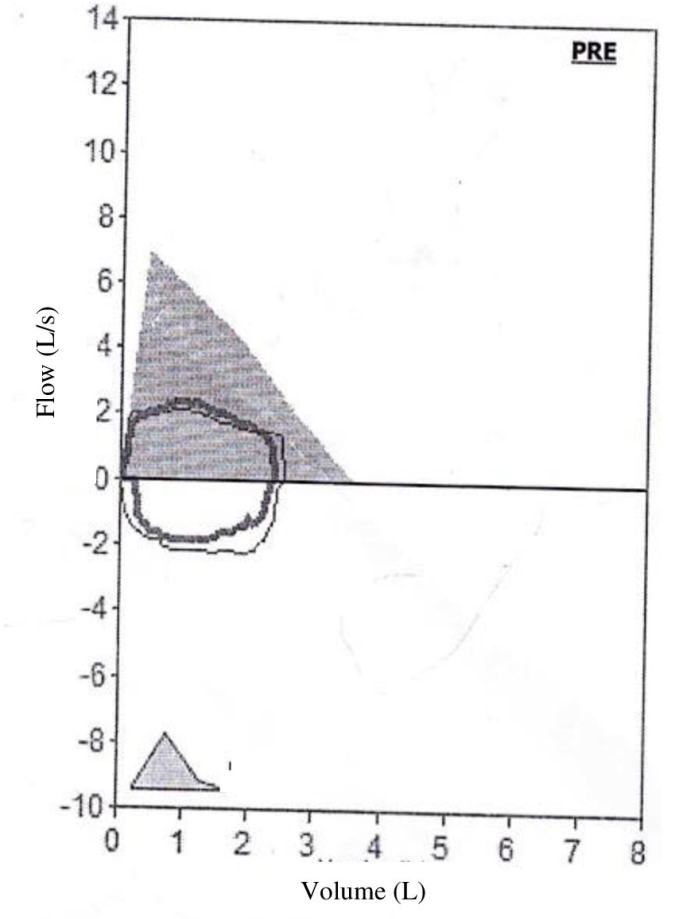

Figure 2. Flow-volume curve showing fixed upper airway obstruction, represented by the characteristic plateau in the inspiratory and expiratory curves.

as acute (less than six weeks) or chronic (recurring or lasting more than six weeks) [2]. Common causes of acute urticaria include allergic factors such as infections, medications, insect bites, and foods, as well as etiologies that directly activate mast cells. Chronic urticaria, which is triggered by physical stimuli like heat, cold, exercise, pressure on the skin, water, vi-

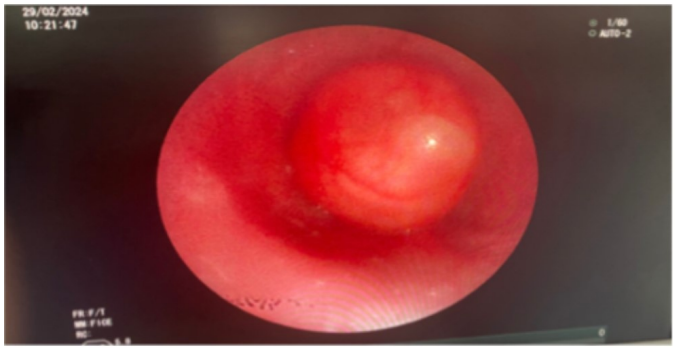

Figure 3. Intraluminal polypoid mass appearance in the trachea at the level of the second cartilage ring during bronchoscopy.

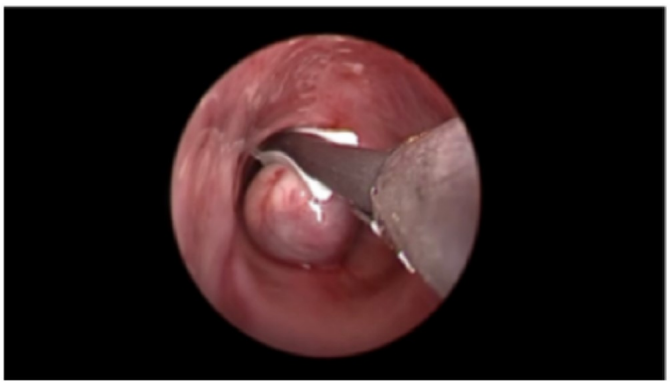

Figure 4. Removal procedure of the polypoid mass occupying 80% of the tracheal lumen at the level of the second cartilage ring.

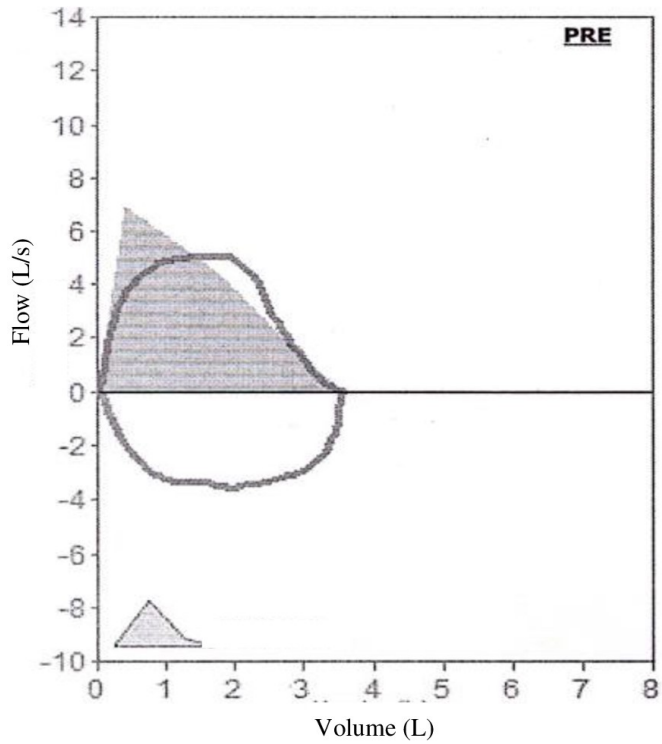

Figure 5. Resolution of fixed upper airway obstruction in the flow-volume curve after lesion removal.

https://doi.org/10.5455/annalsmedres.2025.04.077

bration, or sunlight, is called chronic inducible urticaria. If no physical stimulus is present, it is termed chronic spontaneous urticaria (CSU). CSU has been associated with various allergic causes, thyroid disorders, and autoimmune conditions; however, the relationship between CSU and malignancy remains unclear. Guidelines do not recommend malignant tumor screening unless specific symptoms or findings are present [2-4]. In cases in which urticaria is associated with malignancy, it has been theorized that proteins and hormones secreted by tumor cells may cause urticaria as a part of a neoplastic syndrome [5]. Such cases of urticaria resolve following cancer treatment [6]. However, it is crucial to note that CSU was not determined to increase the risk of malignancy, as reported by a study by Lindelöf et al. [7], which carried out long-term follow-up of 1155 Swedish patients with CSU.

A review of 29 studies involving 6462 patients with CSU identified underlying diseases that could be associated with the condition in only 105 of these patients (1.6%) [8]. Of these, 60 had urticarial vasculitis, 17 had thyroid disease, 7 had lupus, 16 had other connective tissue diseases, 3 had paraproteinemia, 4 had polycythemia vera, and 5 had various malignancies (breast cancer, acute myeloid leukemia, renal cell carcinoma, and two unspecified cancers) as well as other malignancies [8,9]. In a case report by Kartal et al. [10], a patient with urticaria was diagnosed with thyroid papillary cancer, and the regression of urticaria after thyroidectomy emphasized that the association between cancer and urticaria was not a coincidence.

According to the International Urticaria Guidelines, antihistamines (standard dose starting with 1 daily and increasing up to 4) are used as the first step in the treatment of CSU. In unresponsive cases, omalizumab (standard dose 300 mg/4 weeks, but if not sufficient 600 mg/2 weeks) is used as the second step, and in cases that do not respond to these treatments, cyclosporine (5 mg/kg dose) is used as the last step [2]. Although it is not possible to say for sure whether urticaria and PA are directly related in our case, the fact that she did not use antihistamine treatment after the removal of the tracheal lesion and did not have recurrent urticaria suggests a possible connection.

Asthma is a heterogeneous disease characterized by chronic airway inflammation. The condition is defined by symptoms such as wheezing, shortness of breath, chest tightness, and cough, which vary in frequency and time, along with variable expiratory airflow limitation [11]. The diagnosis of asthma is based on characteristic symptoms and the identification of expiratory airflow limitation via pulmonary function testing. Additional tests, including spirometry and laboratory and imaging studies, may be required to confirm asthma or exclude alternative diagnoses that could explain the respiratory symptoms. The goal of asthma treatment includes reducing exacerbations, minimizing permanent airflow limitation, and reducing medication adverse effects. In some patients, asthma control cannot be achieved despite appropriate treatment, and this may necessitate the reassessment of the asthma diagnosis. In our case, HRCT was performed due to uncontrolled asthma despite the Global Initiative for asthma (GINA) step 4 treatment and to investigate the potential common underlying causes (infection, tuberculosis, bronchiectasis, malignancy) for both asthma and urticaria. The patient was diagnosed with a PA in the trachea following advanced investigations prompted by the presence of a tracheal lesion detected on HRCT.

Pleomorphic adenomas (PAs) are typically benign tumors of the salivary glands, though they are also reported in the soft palate, hard palate, upper lip, nasal septum, nasopharynx, orbital region, lower eyelid, buccal mucosa, cheek, external auditory canal, eyelid, and, very rarely, the trachea [8]. A study by Liao et al. examined 29 tracheal PA cases, finding a mean patient age of 48 years (range: 8–83 years) with no sex bias. Over half of these lesions were located in the lower or upper trachea, and the most common symptoms, depending on location, included cough, shortness of breath, stridor, and wheezing [12].

Our patient, a 28-year-old female, presented with stridor, shortness of breath, and wheezing caused by a near-complete obstruction in her upper trachea. PA lesions generally progress over 5.5 months to 10 years; our patient had experienced respiratory symptoms and urticaria for two years. After the lesion's removal, her respiratory symptoms resolved, and the wheezing noted on physical examination completely disappeared. During a 5-month follow-up period, she experienced no recurrence of urticaria.

CONCLUSION

Our case is significant for three reasons: First, the patient presented with urticaria and was diagnosed with a tracheal mass. Second, the symptoms and findings caused by the tracheal mass may have led to a misdiagnosis of asthma, potentially delaying treatment. Third, the PA was found in the trachea, a rare location for this type of tumor. Although PA is a benign tumor, the resolution of urticaria symptoms after excision in our case suggests a possible relationship between PA and urticaria, possibly through unknown tumor-related factors. This case highlights the importance for physicians to reassess patients with asthmatic symptoms who do not respond to advanced treatments, as this is a crucial step in differentiating such rare pathologies.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception: S.Y.; Supervision: N.G.T.; Materials: S.G.; Data Collection and/or Processing: S.G.; Writing: S.Y.

https://doi.org/10.5455/annalsmedres.2025.04.077

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

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

REFERENCES

1. Gaissert HA, Mark EJ. Tracheobronchial gland tumors. *Cancer Control.* 2006 Oct;13(4):286-94. doi: 10.1177/107327480601300406. PMID: 17075566.
2. Zuberbier T, Abdullatiff AH, Abuzakouk M, et al. The international EAACI/GA2LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy.* 2022 Mar;77(3):734-766. doi: 10.1111/all.15090.
3. Powell RJ, Du Toit GL, Siddique N, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy.* 2007; 37:631. doi: 10.1111/j.1365-2222.2007.02678.x.
4. Tedeschi A, Girolomoni G, Asero R, AAITO Committee for Chronic Urticaria and Pruritus Guidelines. AAITO Position paper. Chronic urticaria: diagnostic workup and treatment. *Eur Ann Allergy Clin Immunol.* 2007; 39:225.
5. De P, Abbasi R, Senadhira T, et al. Urticaria and large cell undifferentiated carcinoma of lung. *DOJ.* 2005;11(3). doi: 10.5070/D39gk2f593.
6. Daniel B, Murrell D. Chronic Urticaria Resolving after Resection of Mucinous Breast Cancer. *J Clin Exp Dermatol Res.* 2010;1(103):2. doi:10.4172/2155-9554.1000103.
7. Lindelöf B, Sigurgeirsson B, Wahlgren CF, et al. Chronic urticaria and cancer: an epidemiological study off 1155 patients. *Br J Dermal.* 1990; 123:453. doi: 10.1111/j.1365-2133.1990.tb01449.x.
8. Kozel MM, Bossuyt PM, Mekkes JR, et al. Laboratory tests and identified diagnoses in patients with physical and chronic urticaria and angioedema: A systematic review. *J Am Acad Dermatol.* 2023:48(3)409-16. doi: 10.1067/mjd.2003.142.
9. Chen YJ, Wu CY, Shen JL, et al. Cancer risk in patients with chronic urticaria: a population-based cohort study. *Arch Dermatol.* 2012 Jan;148(1):103-8. doi: 10.1001/archdermatol.2011.682.
10. Kartal O, Abdullah B, Ramazan E, Mustafa G, Zafer C, Osman S. Acute urticaria associated with thyroid papillary carcinoma: a case report. *Ann Dermatol.* 2012 Nov;24(4):453-4. doi: 10.5021/ad.2012.24.4.453.
11. Global Initiative for asthma (GINA). Global strategy for asthma management and prevention; 2023 (Available at: www.ginasthma.org. Accessed on: 17.07.2023).
12. Liao, Qian-Nuan, et al. "Pleomorphic adenoma of the trachea: A case report and review of the literature. *World J Clin Cases.* 2020 Dec 6;8(23):6026-6035. doi: 10.12998/wjcc.v8.i23.6026.

https://doi.org/10.5455/annalsmedres.2025.04.077