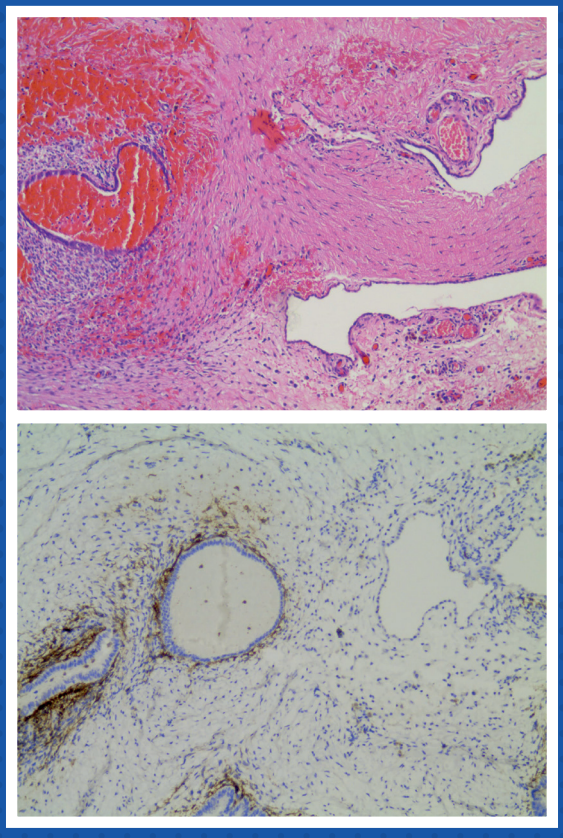
ISSN: 2979-9538

NORTHWESTERN MEDICAL JOURNAL

Year: 2025 ▪ Volume: 5 ▪ Issue: 1



Official Journal of Izzet Baysal Training and Research Hospital

NORTHWESTERN MEDICAL JOURNAL

Year: 2025 ▪ Volume: 5 ▪ Issue: 1

ISSN: 2979-9538

www.nwmedj.org

Official Journal of Izzet Baysal
Training and Research Hospital

Northwestern Medical Journal

ISSN: 2979-9538 (Online)

Owner
Owner on behalf of the Bolu İzzet Baysal Training and Research Hospital
Prof. Mervan Bekdaş, MD
Director, Bolu İzzet Baysal Training and Research Hospital, Türkiye

Publication Type
International peer-reviewed journal

Publication Frequency and Language
Quarterly (January, April, July, October), English

Abstracting and Indexing
Northwestern Medical Journal indexed in TR Index, DOAJ, GALE, J-Gate, and TürkMedline.

Editor in Chief
Prof. Ahmet Ural, MD
Bolu Abant Izzet Baysal University, Faculty of Medicine, Department of Otorhinolaryngology, Head & Neck Surgery, Türkiye

Publisher
Izzet Baysal Training and Research Hospital

Publisher Address
Izzet Baysal Training and Research Hospital, Gölköy 14280 Bolu, Türkiye
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E-mail: nwmedj@gmail.com
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Northwestern Med J. 2025;5(1):1-8
DOI: 10.54307/NWMJ.2025.140

RESEARCH ARTICLE

The effect of cable fixation on union time in subtrochanteric femur fractures treated with cephalomedullary nailing

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Cite as: Can Fİ, Gültaç E, Kılınç RM, Kılınç CY. The effect of cable fixation on union time in subtrochanteric femur fractures treated with cephalomedullary nailing. Northwestern Med J. 2025;5(1):1-8.

ABSTRACT

Aim: This study aimed to examine the effect of cable cerclage on reduction quality and union time in patients treated with cephalomedullary nails for subtrochanteric fractures.

Materials and Methods: 75 closed subtrochanteric fractures treated with cephalomedullary nails by two different surgeons with at least 10 months of follow-up were included in the study. Patients operated by Surgeon 1 were grouped as Group 1 (closed cephalomedullary nailing without cables, n=43), patients operated by Surgeon 2 with 1-2 cables as Group 2 (n=20), and those operated with 3-4 cables were grouped as Group 3 (open cephalomedullary nailing + cable fixation, n=12). Postoperative radiographs were evaluated for the presence of cables, the number of cables used, deformity, the residual gap between the fracture ends, and the union time.

Results: The cable fixation rate was calculated as 42.6%. There was a statistically significant relationship between cable use and the amount of gap (p=0.033). The average gap was 3.97 mm in patients without cables, 0.65 mm in patients with 1-2 cables, and 0.66 mm in patients with 3-4 cables. A positive correlation was found between the amount of gap and the time to union (Spearman's rho= 0.468, p=0.001). A statistically significant difference was found between Group 1 and Group 2 and also between Group 1 and Group 3 regarding the union time (p=0.007, p=0.001, respectively). The mean time to union was determined as 7.3 months in Group 1, 5.4 months in Group 2, and 5.7 months in Group 3.

Conclusion: Reducing the gap in the fracture line by using cables provides a better reduction, stability, and a shorter union time than fixation without a cable in subtrochanteric fractures treated with cephalomedullary nailing.

Keywords: subtrochanteric fractures, cephalomedullary nailing, cable fixation, residual gap, union time

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Received: 17.07.2024 **Accepted:** 13.12.2024 **Published:** 31.01.2025

INTRODUCTION

Intramedullary nailing is an ideal technique for the treatment of lower extremity long bone fractures because of its feasibility and high union rates (1,2). In subtrochanteric fractures, cephalomedullary nails are frequently used for treatment (3). However, reduction and fixation difficulties are frequently encountered in subtrochanteric fractures due to abduction, flexion, and external rotation deformities caused by the psoas, abductor, and gluteal muscles attached to the proximal part of the fracture (4,5). There is a literature regarding a faster and better union of subtrochanteric fractures. While some authors advocate closed reduction to not deteriorate the fracture hematoma, others emphasize the need to provide as much anatomical alignment as possible and the benefits of cerclage cables (6-10).

Due to the improper position of the proximal part of the fracture, the lateral entry point of the cephalomedullary nail causes varus deformity (11). Angular malreduction may develop in patients with the closed reduction due to strong muscle tone affecting the proximal part and the proximal medullary canal being relatively wide compared to the distal isthmus, and this may cause gap formation between the fracture ends, loss of fixation or implant failure (4,12). For these reasons, the question of which technique - hematoma-preserving closed reduction or open reduction with cable fixation - is more advantageous for subtrochanteric nailing remains unanswered. The reduction quality is of great importance to properly distribute the axial forces to the nail and femoral cortex. The aim is to prevent the entire load from getting on the nail and to allow the femoral cortex to share the axial load (13,14). Proper alignment before placing the nail reduces the possibility of complications (15-17).

Our aim in this study is to examine the effects of factors such as the amount of residual gap at the fracture line, the use of cables, and the number of cables on the union time of subtrochanteric fractures treated with cephalomedullary nails. We believe that the improvement in surgical technique after identification of these factors will not only be very effective in preventing complications such as delayed union, nonunion, malalignment, and implant failure, but will also provide a shorter union time.

MATERIALS AND METHODS

The study was designed in accordance with the 1995 Helsinki Declaration. Approval for this study was granted by the local ethics committee. Preoperative and postoperative radiographs of 229 patients aged 18-89 years who underwent surgery for subtrochanteric fractures at our clinic between March 2010 and February 2018 by two different surgeons were retrospectively evaluated. Patients over the age of 65 (n= 40), who had plate and screw fixation (n=43), who received bisphosphonate therapy for more than 1 year (n=11), who had insufficient postoperative follow-up (n=41), who died during the follow-up period (n =19) were excluded from the study. Seventy-five patients with a mean age of 48.3 (range 19-65) who had at least 10 months of follow-up and who had been operated on with a cephalomedullary nail were included in the study (Figure 1).

Demographic data of the patients, such as age and gender, were compiled. Fracture classification was made according to Seinsheimer's classification by evaluating preoperative anteroposterior (AP) femur roentgenograms (13). By evaluating the postoperative films, it was determined whether a titanium cable was placed and if so, how many were utilized. Patients

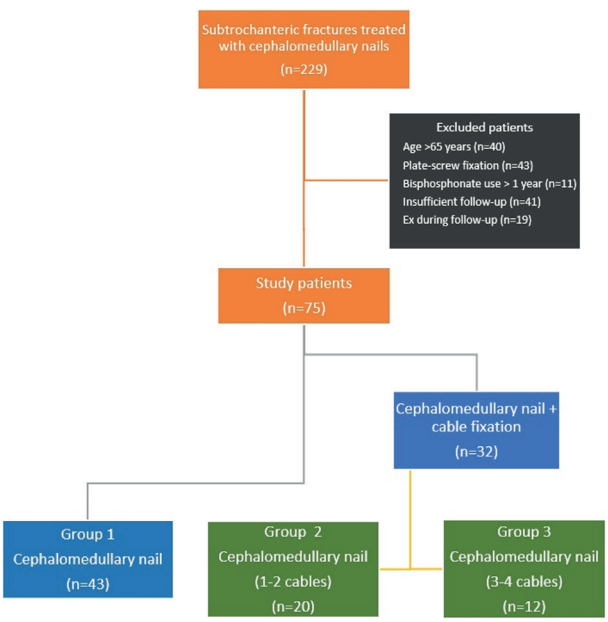

Figure 1. Flowchart of patient selection.

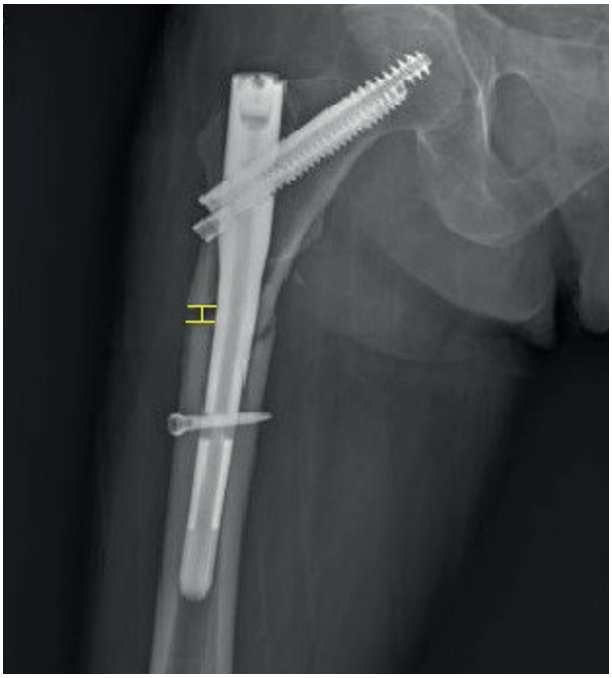

Figure 2. The measurement of the gap between fracture lines.

operated by Surgeon 1 were grouped as Group 1 (closed cephalomedullary nailing without cables, n=43), patients operated by Surgeon 2 with 1-2 cables as Group 2 (n=20), and those operated by Surgeon 2 with 3-4 cables were grouped as Group 3 (open cephalomedullary nailing + cable fixation, n=12). The medial or lateral gap between the fracture ends was evaluated by an experienced radiologist using the "Picture Archiving and Communication System" (PACS) and the amount of gap was measured (Figure 2). While measuring the gap between the fracture ends, the distance between the fracture ends on the medial or lateral wall with cortical discontinuity was evaluated using postoperative AP X-rays. The deformity was measured in degrees by determining the presence of varus or valgus deformity. Early postoperative x-rays and x-rays after the union were used for the measurements. The development of varus deformity was compared using early postoperative radiographs and radiographs taken after union (Figure 3 and 4). It was investigated whether there was a statistically significant difference between the groups in terms of age, gender, fracture type, union time, varus

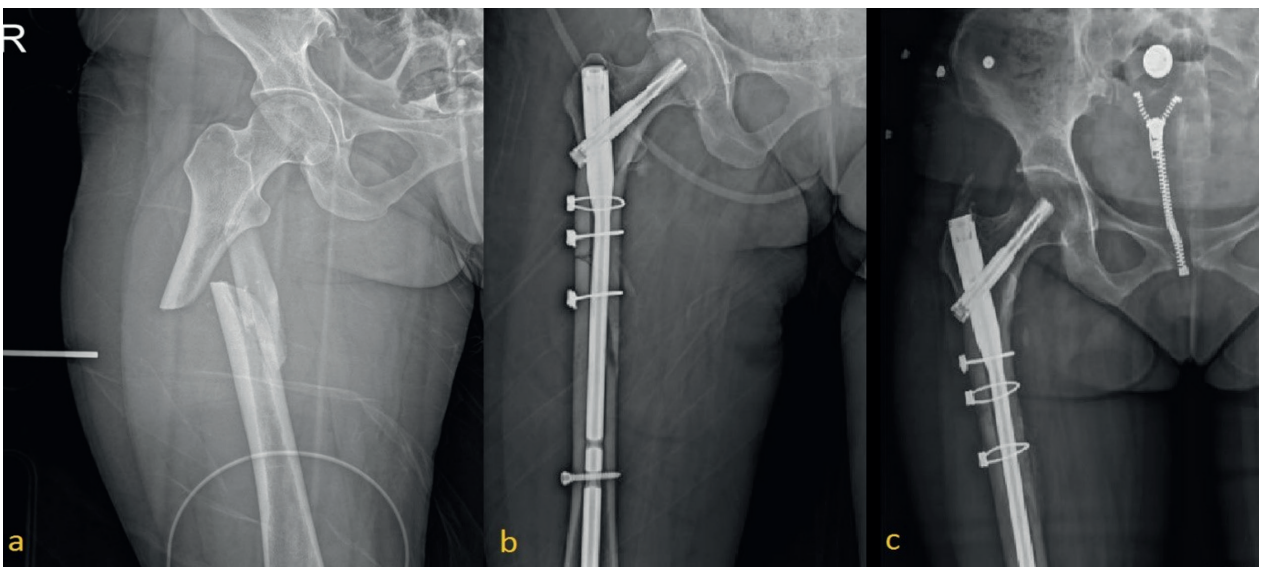

Figure 3. a) 70 years old female patient, motor vehicle accident, preoperative x-ray. **b)** Postoperative 7th month x-ray, 7mm gap laterally and 6 degrees of varus deformity. **c)** 6th month x-ray after revision surgery with cable use, complete union.

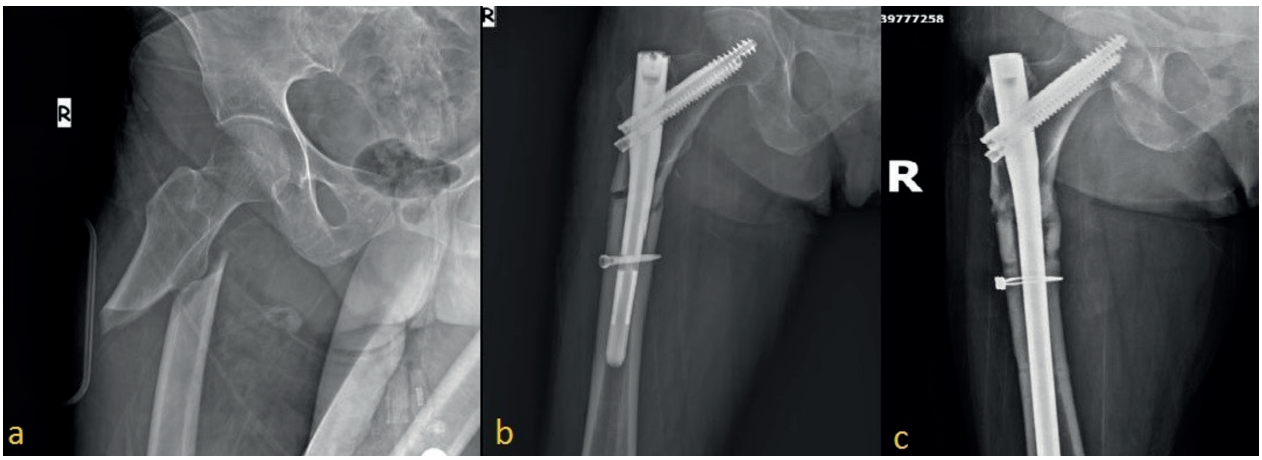

Figure 4. a) 37 years old female patient, motor vehicle accident, preoperative x-ray. **b)** Postoperative 1st month x-ray, fixation with 3 cables, 3 mm gap laterally. **c)** Postoperative 5th month, complete union.

angulation, and gap size. The need for revision surgery due to non-union was also noted.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows v.22 (IBM Corp., Armonk, NY, USA) software. Demographic data and numerical measurements were determined to be non-normally distributed according to the distribution analysis, and non-parametric tests were used. Statistical analysis between union groups was assessed using the Kruskal-Wallis test. A pairwise comparison test was used to determine which group caused the significant difference between the groups. Correlation between numerical data was analyzed with Spearman's rank correlation coefficient test. P-value <0.05 was considered statistically significant.

RESULTS

26 (34.7%) patients were female and 49 (65.3%) were male. The mean follow-up period was 12.33 months (10-17 months). There was no statistically significant difference between the groups in terms of demographic data such as age and gender (p=0.139, p=0.954, respectively).

According to the Seinsheimer's classification, the fractures were classified as Type 1 (n=6), Type 2A (n=7), Type 2B (n=4), Type 2C (n=10), Type 3A (n=9), Type 3B (n=9) Type 4 (n=15) and Type 5 (n=15). No statistically significant relationship was found between fracture types and study groups (p=0.065) (Table 1).

Cables were used in 32 of the 75 patients. There was a statistically significant relationship between cable use and the amount of residual gap (p=0.033). The average residual gap was 3.97 mm (range 0-11 mm) in patients without cables, 0.65 mm (range 0-4 mm) in patients with 1-2 cables, and 0.66 mm (range 0-3

Table 1. Distribution of fracture types according to Seinsheimer's classification

Fracture Type	Number of Cases (n)
Type 1	6
Type 2A	7
Type 2B	4
Type 2C	10
Type 3A	9
Type 3B	9
Type 4	15
Type 5	15

Table 2. The results of each group created according to cable usage

	Cable use	Patient Number	Gap Size (mm) (mean-min-max)	Mean union time (mos)	Varus deformity (n)
Group 1	0	43	3.97 - 0 - 11	7.3	9
Group 2	1-2	20	0.66 - 0 - 4	5.4	1
Group 3	3-4	12	0.65 - 0 - 3	5.7	-

min: minimum, max: maximum, mos: months, n: number.

mm) in patients with 3-4 cables (Table 2). A positive correlation was found between the amount of gap and the time to union (Spearman's rho= 0.468, p=0.001).

A statistically significant difference was found between Group 1 and Group 2 and also between Group 1 and Group 3 regarding the union time (p=0.007, p=0.001, respectively). The mean time to union was measured as 7.3 months in Group 1, 5.4 months in Group 2, and 5.7 months in Group 3 on average. No statistically significant relationship was found between study groups and gender (p=0.847).

Varus deformity (between 4-12 degrees) was detected in 10 patients. The cable was not used in 9 out of 10 patients who developed varus deformity. There was no statistically significant relationship between varus deformity and union times between the groups (p=0.201). Four patients received revision surgery due to nonunion.

DISCUSSION

Subtrochanteric fractures are generally the result of high-energy trauma in young patients and low-energy trauma due to poor bone quality in elderly patients (15). In subtrochanteric fractures, cephalomedullary nails are frequently used for treatment (3). Cephalomedullary nailing is a method with biological and biomechanical advantages due to its percutaneous application, load-sharing ability, and short-moment arm.

In subtrochanteric fracture surgery, reduction and fixation difficulties are frequently encountered due to muscle forces deforming the proximal fracture segment. The use of cable is also a highly preferred method to improve reduction quality and fixation stability (2). The possibility of damage to the nutritional vascular structures of the femur due to the pressure exerted by the cables and the occurrence of union disorders due to nutritional deficiency is a very thought-provoking problem for surgeons. A review of the literature reveals that there is no consensus among the authors about the effect of cable use on bone nutrition. Recent anatomical and histological studies have reported that the femoral arterial circulation is circular rather than longitudinal (18-21). Apivatthakakul et al. also showed that macrovascular nutrition was preserved after cable application in a cadaver study, and they reported that cerclage wiring caused minimal disruption of the femoral blood circulation (22). Kennedy et al. stated that one or two cables do not impair circulation and can be used in spiral oblique fractures due to the circular arterial placement in the bone (6). In a biomechanical study by Müller et al. on cadavers with subtrochanteric fractures, the cerclage group and the non-cerclage group were compared, and it was emphasized that the use of cables not only provides a satisfactory reduction, but also preserves the integrity of the medial cortex, and reduces the risk of nonunion and fixation loss (23). Shin et al. stated that cerclage cable fixation increases the possibility of anatomical reduction and better stability while preserving the biology around the fracture line, and emphasized that the cerclage cable method is effective in subtrochanteric fractures. In this study, in which 51 patients who underwent intramedullary nailing and percutaneous cerclage were examined, the authors recorded the postoperative angulation as a maximum of 5 degrees and reported union at a rate of 98% (24). Liu et al. In their study in which they presented the treatment of 46 subtrochanteric femur fractures with cable cerclage and intramedullary nailing, they reported the mean time of union as 3-6 months and stated that they provided good and excellent union at a rate of 86.96%. They reported that the use of cables not only provides a good alignment but also increases stability (25). In a

study by Mukherjee et al., 40 composite femurs that underwent subtrochanteric osteotomy were analyzed and it was reported that cable application on the nail increases stability in subtrochanteric fractures (26). Similarly, another study that retrospectively analyzed 260 patients reported that additional cerclage application on the nail increased the possibility of anatomical reduction, contributed to the stability, and positively affected union by providing extra support to the medial cortex. It has also been stated that better clinical results are obtained in cases with cerclage compared to applications without cerclage and this application is a very useful support method in comminuted trochanteric and subtrochanteric fractures (5).

In our study, when the relationship between cable use and the union was examined, it was determined that the union time was shorter in patients with cable use compared to patients operated without cable fixation, and the amount of residual gap in the fracture line was less with the cable fixation. No study has been found in the literature showing the relationship between the amount of gap of the fracture ends and the duration of the union in patients treated with cephalomedullary nails. In our study, there was a statistically significant relationship between cable use and the amount of gap (p=0.033). The average gap was 3.97 mm (range 0-11 mm) in patients without cables, 0.65 mm (range 0-4 mm) in patients with 1-2 cables and 0.66 mm (range 0-3 mm) in patients with 3-4 cables. In addition, a positive correlation was found between the amount of gap and union time (Spearman's rho= 0.468, p=0.001). The cable fixation of the fracture fragments is more stable, the anatomical alignment of the bone is better, and ultimately less gap is formed at the fracture line during reduction. It is widely accepted in the literature that ensuring the best possible alignment and leaving less gap at the fracture line are important factors that facilitate and accelerate the union of the subtrochanteric fractures.

One of the important problems that can be seen after fixation in subtrochanteric fractures is varus deformity (13,27-29). There are many studies in the literature investigating the relationship between varus deformity and delayed union and non-union (3,30,31). In the study by Ostrum et al., excessive lateralization of the trochanter major entry point was presented as an important cause of varus deformity (11). The study by Hoskins et al. reported that there was an increase in varus deformity when anatomical reduction could not be achieved (31). In our study, we observed that 90% of the 10 varus deformities we encountered developed in patients who didn't have cable fixation. While providing a more stable reduction of the fracture fragments, cables also help to maintain stabilization in the postoperative follow-up period. Recently, Recently, there has been debate in the literature as to whether hematoma integrity or stability is more effective for fracture union. Although our study does not allow interpretation of hematoma integrity, it is quite supportive of the importance of stability.

The most important limitation of our study is its retrospective nature. Apart from this, there are other limiting factors such as the age, gender, and trauma severity of the patients, which were not homogeneously distributed, and the use of different nails by many surgeons can be counted. Despite these shortcomings, we believe that our study provides a strong conclusion and sufficient statistical data.

CONCLUSION

Our study demonstrated that in subtrochanteric fractures treated with cephalomedullary nailing, reducing the gap in the fracture line by using cable wires provides a better reduction, stability, and a shorter union time than fixation without using cable(s).

Ethical approval

This study has been approved by Muğla Sıtkı Koçman University Ethical Commitee (approval date 21/07/2020, number 158). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: CYK; Concept: CYK; Design: FİC; Data Collection or Processing: EG; Analysis or Interpretation: RMK; Literature Search: FİC; Writing: FİC. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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NORTHWESTERN MEDICAL JOURNAL

Northwestern Med J. 2025;5(1):9-15
DOI: 10.54307/NWMJ.2025.99

RESEARCH ARTICLE

Diaphragmatic crus indentation to the renal artery: Is it a new etiology for renovascular hypertension in adults?

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Cite as: Akkurt Acar D, Çilengir AH, Balaban M, Çamur E, Akdal Dölek B, Işıksalan Özbülbül N. Diaphragmatic crus indentation to the renal artery: Is it a new etiology for renovascular hypertension in adults? Northwestern Med J. 2025;5(1):9-15.

ABSTRACT

Aim: To investigate the relationship between hypertension and the indentation and compression of the diaphragmatic crus in the renal artery.

Material and Methods: Abdominal computed tomography scans of 304 consecutive adult patients performed for any reason were retrospectively analyzed. Patients with crus indentation or compression on the renal artery were identified. Diaphragmatic crus contact was defined as compression if it caused stenosis more than 50% of the renal artery diameter, and indentation if it caused stenosis less than 50%. If the renal artery originated above the level of the L1-2 intervertebral disc, it was considered as a high origin.

Results: The mean age of women was 51±15.29 and the mean age of men was 52±15.38. Hypertension was present in 29.6% (n=74) of the patients. Diaphragmatic crus indentation (DCI) was detected in 8.4% (n=21) of all patients, and 76.2% (n=16) of these were men. Diaphragmatic crus compression (DCC) (n=3) was detected in 1.2% of all patients, and 67% (n=2) of these were women. Hypertension was present in 67% (n=2) of patients with DCC, all of them were women, and the mean age was 65.5 years. Hypertension was present in 38.1% (n=8) of patients with DCI.

Conclusions: DCI and DCC which can be caused by hypertrophic diaphragmatic crus or high origin of the renal artery, should be included in the etiology of renovascular hypertension. In addition to the presence of renal artery stenosis in a patient with hypertension, the relationship between the renal artery and diaphragmatic crus should also be evaluated.

Keywords: diaphragmatic crus, hypertension, renal artery, renovascular

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Received: 04.03.2024 **Accepted:** 07.06.2024 **Published:** 31.01.2025

INTRODUCTION

Diaphragmatic crura are musculotendinous structures that connect the posterior and middle parts of the diaphragm to the lumbar vertebrae. The right crus attaches to the L1-L3 vertebral body, and the left crus attaches to the L1-L2 vertebral body. Since anomalies affecting the diaphragmatic crura are often asymptomatic, they are usually detected incidentally during imaging (1,2).

Direct radiography, fluoroscopy, ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) are used for imaging the diaphragm. Compared to US, CT is more successful in demonstrating diaphragmatic anatomy and diaphragm-related lung-mediastinum pathologies (3,4). CT is also quite successful in measuring diaphragmatic crus thickness, which is a critical indicator for the evaluation of the pacemaker insertion system in patients with amyotrophic lateral sclerosis, the diagnosis of unilateral diaphragm paralysis, sepsis, and diaphragmatic atrophy due to mechanical ventilator therapy (5-8).

Diaphragmatic crus compression on the renal artery is primarily documented in case reports within the literature, and its incidence remains unclear (9-11). The available studies on renal artery compression have evaluated the origin level of the renal arteries, but have not investigated the incidence of the diaphragmatic crus indentation on the renal artery and accompanying hypertension. We also hypothesized that indentation, unlike compression on the renal artery, may also cause renovascular hypertension. In this analysis, we aimed to investigate the relationship between indentation and compression of the diaphragmatic crus on the renal artery, and hypertension in the adult age group.

MATERIAL AND METHODS

This case-control study was carried out between June – October 2020. The Institutional Review Board approved the survey in terms of ethical suitability (Date: 09.03.2022, Number: E1-22-2407).

Study population

Abdominal CT scans of 304 consecutive adult patients performed for any reason were retrospectively analyzed. Patients with ectopic or solitary kidney (n=10), aortic aneurysm (n=5) or dissection (n=4), severe chronic obstructive pulmonary disease (n=8), and a mass causing invasion/displacement in the diaphragmatic crus (n= 3), rotoscoliosis (n=7), and patients whose images could not be evaluated due to motion artifacts (n=17) were excluded. A total of 250 patients (107 women, 143 men) were included. The clinical and demographic information and CT images of the patients were accessed from the hospital automation system.

Image acquisition

The dynamic protocol was performed on a 512-slice CT scanner (Revolution, GE Healthcare, Waukesha, WI, USA) using the parameters 120 kV, 100 mAs, pitch 0.9, rotation time 0.6 sec, 80 mm. For contrast-enhanced imaging, 90 ml of contrast agent was administered via an automatic injector at a rate of 5 ml/sec from the left antecubital vein while the patient was lying in the supine position. 40 ml of 0.9% saline was administered after contrast agent injection at the same rate. Images were acquired in the arterial, portal, and venous phases (with fixed delay time or SmartPrep).

Measurements

Diaphragmatic crus thickness was measured on the axial slice at the level of the superior mesenteric artery (Figure 1). The diameters of the renal arteries were measured on the arterial phase axial slices at 1 cm distal from their origins with 100% magnification. Patients with crus indentation or compression on the renal artery were identified. Diaphragmatic crus contact was considered as compression if it caused stenosis greater than 50% of the renal artery diameter (Figure 2), and indentation if it caused stenosis less than 50%. If the renal artery originated from a higher than L1-2 intervertebral disc level, it was considered a high origin. Additionally, accompanying renal parenchymal abnormalities were noted. Measurements were made by an abdominal radiologist (D.A.). The presence of hypertension, and whether there was another cause of hypertension, was determined by the hospital's

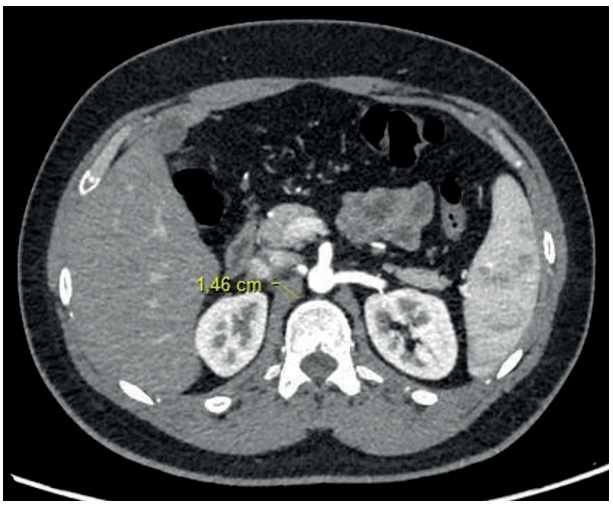

Figure 1. Right diaphragmatic crus thickness measurement on the axial slice at the level of the superior mesenteric artery.

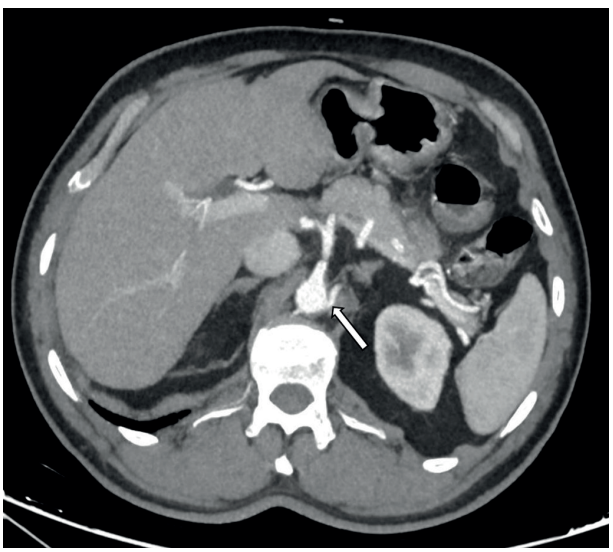

Figure 2. Maximum intensity projection of the axial plane computed tomography image shows the narrowing of the left renal artery orifice (arrow) secondary to the diaphragmatic crus compression.

automated registration system. Blood pressure higher than 140/90 mmHg was considered as hypertension. Estimated glomerular filtration rate (eGFR), serum creatinine level, and accompanying imaging findings were also noted.

Statistical analyses

Data were evaluated using IBM Statistics 22.0 (IBM Corp. Armonk, NY, USA). Frequency tables and descriptive statistics were used to interpret the findings. The relationship between two qualitative variables, and the expected value levels were analyzed by the Fisher-Exact and Pearson-$\chi 2$ test. The Mann-Whitney U test (Z-table value) was used to compare the measurement values of two independent groups. A p-value less than 0.05 was accepted as statistically significant.

RESULTS

The mean age of women was 51±15.29 (range: 18-86 years) and the mean age of men was 52±15.38 (range: 18-84 years). The mean age of patients with diaphragmatic crus compression (DCC) and/or indentation (DCI) was 48.46±15.13 years, while the mean age of those without was 52.04 ±15.33 years (p=0.237). Hypertension was present in 29.6% (n=74) of the patients. There were 45 men (60.8%) and 29 women (39.2%) with hypertension. In contrast, 99 men (55.9%) and 78 women (44.1%) did not have hypertension. The right side was affected in all patients with DCC (n=3).

DCI was on the right side in 81% (n=17), on the left in 9.6% (n=2), and bilateral in 9.6% (n=2). Diaphragmatic crura thicknesses in the group with and without diaphragmatic indentation were summarized in Table 1. Ipsilateral crus was found to be thicker in patients with DCI (p=0.004). DCI was detected in 8.4% (n=21) of all patients, and 76.2% (n=16) of these were men. DCC (n=3) was detected in 1.2% of all patients, and 67% (n=2) of these were women. Hypertension was present in 67% (n=2) of patients with DCC, all of them were women, and the mean age was 65.5 years. Hypertension was present in 38.1% (n=8) of patients with DCI, all of them were men, and the mean age was 46.8 years.

The distribution of the patients with DCC – DCI in the high-origin renal artery and hypertension groups is summarized in Figure 3. In 2 patients with DCC and hypertension serum creatinine level was normal,

Table 1. Bilateral diaphragmatic crus thicknesses (in millimeters) at the superior mesenteric artery level in patients with and without diaphragmatic crus indentation or compression

	Diaphragmatic Crus Thickness (Mean ± Standard Deviation)		
	Patients with Crus Indentation (n=21)	**Patients with Crus Compression (n=3)**	**Patients without Crus Indentation or Compression (n=226)**
Right Crus	8.70 ± 2.05	9.90 ± 3.77	7.72 ± 5.96
Left Crus	6.75 ± 2.25	6.26 ± 3.05	6.26 ± 3.07

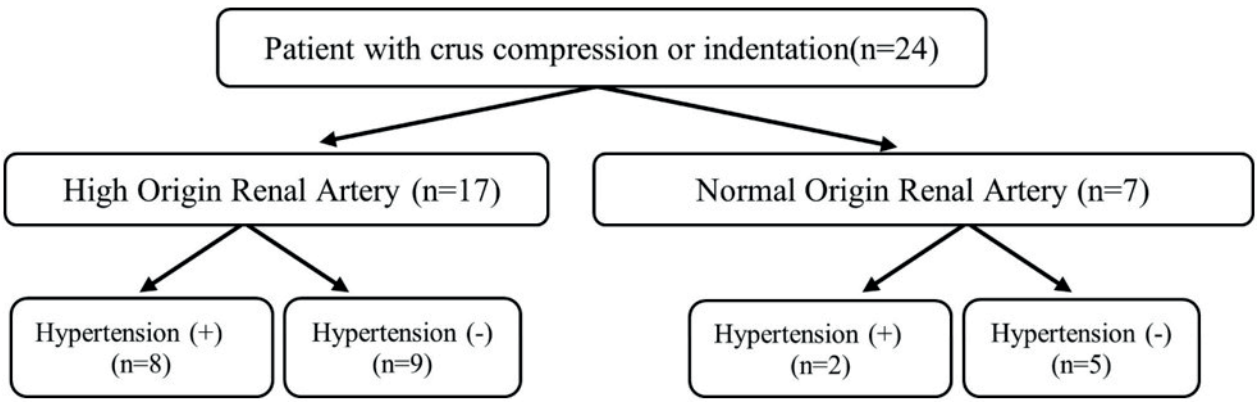

Figure 3. The distribution of the patients with diaphragmatic crus compression or indentation in renal artery origin and hypertension groups.

but their eGFR was 79 ml/min and 80 ml/min which is slightly lower than normal (normal>90 ml/min). While serum creatinine level and eGFR were normal in 4 of 8 patients with DCI and hypertension, serum creatinine level was normal in 2 patients, but GFR was at the lower limit (90 ml/min). There was one patient, whose serum creatinine level was 1.27 mg which is slightly higher than normal, eGFR was 72 ml/min, and there was decreased activity uptake at Tc-99m-DMSA scintigraphy of the right kidney. Additionally, there was one patient, whose serum creatinine level was 5.38 mg and eGFR was 11ml/min which was consistent with renal failure. In 3 patients with DCI without hypertension, serum creatinine levels were normal but eGFR was slightly low (76 ml/min, 89 ml/min, and 82 ml/min).

DISCUSSION

In our study investigating the relationship between DCI and DCC in the renal artery and renovascular hypertension, DCI was detected more frequently than DCC. DCC and DCI were more common on the right side in our study population. The ipsilateral crus was found to be significantly thicker in patients with DCI, and most were men. The frequency of hypertension, female sex, and mean age were higher in patients with DCC.

Hypertension is arterial blood pressure that is consistently 130/80 mmHg or higher (12). Hypertension caused by any pathology in the renal artery is called renovascular hypertension. Color Doppler US, CT angiography, and magnetic resonance angiography (MRA) are used to diagnose renovascular hypertension. Color Doppler US is the first diagnostic tool for detecting the etiology of hypertension because it is accessible and cheap. Peak systolic velocity in the renal artery>180-200 cm/sec and/or reno-aortic ratio>3 indicate renal artery stenosis (RAS). Indirect findings of RAS are prolongation of acceleration time (>70msec) in segmentary branches of the renal artery and tardus parvus waveform distally from the stenosis (13). Obesity, the patient's breathing noncooperation, and abdominal bowel gas are limitations of this

method. Contrast-enhanced MRA has a sensitivity and specificity of 90% in detecting RAS (14,15). Due to the renal toxicity of the iodinated contrast agents, MRA is often preferred in patients with renal failure for detecting RAS. CT angiography perfectly reveals the vascular anatomical structure with multiplanar images. The sensitivity and specificity of CT angiography in the diagnosis of RAS vary between 67-100% and 77-98%, respectively (16,17). It provides excellent anatomical orientation, visualization of the surrounding tissues of the renal artery, and 3-dimensional reconstruction.

The incidence of hypertension secondary to RAS is around 1% (18). The most common cause of RAS in children and young adults is fibromuscular dysplasia, on the other hand, the most common cause in middle-aged adults is atherosclerosis (19). Other causes of RAS include aortic dissection, arteritis, congenital malformations, extrarenal masses compressing the renal arteries, diaphragmatic crus compression/ indentation, and thromboembolism.

DCI and DCC have been reported in case reports in the literature, and their exact frequency is not known (9-11). DCC was first described by D'Abreu in two surgical cases in 1962 (20). There is a case series of three cases of renal artery compression by the fibromuscular band. It was reported in this study that one of the three bands originated from the diaphragm, while the other two were from the sympathetic aortorenal plexus (21). Rather than mechanical compression, sympathetic ganglion compression on the renal artery may be effective in the hypertension cascade (21). In line with all this information, we found the incidence of DCI was 8.4% among 250 patients and hypertension was accompanied by 38.1% of them. The fact that the DCI ratio is less than the hypertension ratio supports that the indentation of the diaphragm crus on the renal artery is not only related to the renal artery but may also be related to the compression of the sympathetic plexus.

Thony et al. (9) detected DCC in 15 patients in their study. They reported that 73% of these cases were on the right side, 53% had crus hypertrophy, and 40% had high-origin renal artery. In our study, we found that the crus on the same side was thicker in patients with DCI ($p=0.004$).

The high origin of the renal artery has been reported as an important cause of DCC in the literature and is more common on the left side (9,22-25). It is thought to be due to an anomaly during the migration of the kidney (10). In our study, the majority of patients (n=8) (87.5%) with DCI had a high origin of the renal artery. Four patients were on the right side, one patient was on the left side, and two patients had a bilaterally high origin. Ozkan et al. (26) revealed that 98% of renal arteries originate from any level between the L1 vertebra superior end plate and the L2 vertebra inferior end plate in their study. In our study, 71.4% of the patients with DCI had a high origin of the renal artery, and the origin of the renal artery was above the L1-L2 intervertebral disc.

Since CT scans of our patients were not performed to detect the etiology of hypertension, the laboratory data of some patients are not available in the automation system. Therefore, we could not make a detailed evaluation of renovascular hypertension in terms of laboratory findings. Other limitations of our study include the possibility of exaggerated stenosis, and the lack of color Doppler US to correlate stenosis.

The present study has several limitations. The first limitation was the retrospective design and relatively small number of patients. Due to the retrospective design, we could not perform any additional diagnostic tests for the etiology of the renovascular hypertension. Since CT scans were performed in the supine position with deep inspiration, there might have been an exaggeration of the indentation or compression.

In conclusion, DCI and DCC which can be caused by hypertrophic diaphragmatic crus or high origin of the renal artery, should be included in the etiology of renovascular hypertension. Although hypertension was detected more frequently than DCI in patients with DCC, the frequency of DCI was higher in our study. Therefore, even if there is no compression of the renal artery, the interaction of the renal arteries with the diaphragmatic crus should be kept in mind for patients with hypertension.

Ethical approval

This study has been approved by the Ankara City Hospital Review Board (approval date 09.03.2022, number E1-22-2407). Written informed consent was obtained from the participants.

Author contribution

Concept: DAA, NIÖ; Design: DAA, NIÖ; Supervision: AHÇ, MB, NIÖ; Materials: DAA, EÇ, BAD; Data Collection and/or Processing: DAA, EÇ, BAD; Analysis and/or Interpretation: DAA, EÇ, BAD; Literature Search: DAA, EÇ, BAD; Writing Manuscript: DAA, AHÇ, MB, EÇ, BAD, NIÖ; Critical Review: MB, AHÇ, NIÖ. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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NORTHWESTERN MEDICAL JOURNAL

Northwestern Med J. 2025;5(1):16-24
DOI: 10.54307/NWMJ.2025.77

RESEARCH ARTICLE

The prognostic value of neutrophil-to-lymphocyte ratio in nasopharyngeal cancer

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Cite as: Kandaz M, Balsak A, Çobanoğlu HB. The prognostic value of neutrophil-to-lymphocyte ratio in nasopharyngeal cancer. Northwestern Med J. 2025;5(1):16-24.

ABSTRACT

Introduction: The prognostic value of the neutrophil-to-lymphocyte ratio (NLR) for nasopharyngeal carcinoma (NPC) continues to be debated. This study was conducted to enhance the accuracy of its prognostic value through a single-centre analysis.

Methods: Ninety-seven patients with NPC who received adjuvant radiotherapy between 1998 and 2022 were analyzed retrospectively.

Results: The study included a total of 97 patients who were treated for NPC and had available data. In 54 (56%) patients the NLR was ≤3 and in 43 (44%) the NLR was >3. The mean age of the patients was 49.64±14.51 (range: 12-82) years. Four patients were ≤18 years old and 93 patients were >19 years old. Sixty-three (65%) patients were male, 34 (35%) patients were female. For stage I patients, NLR was ≤3 in 2 (2%) and >3 in 2 (2%) patients. For stage II patients, NLR was ≤3 in 10 (11%) and >3 in 8 (8%) patients. For stage III patients, NLR was ≤3 in 29 (30%) and >3 in 25 (26%) patients. For stage IVA patients, NLR was ≤3 in 12 (12%) and >3 in 8 (8%) patients. For stage IVB patients, NLR was >3 in 1 (1%). The follow-up period was 79.4±72.1 (2-279) months. In all patients, mean overall survival (OS) was 159.37±13.66 (132.97-185.76) months, median 205±31.11 (144-265.99) months, The 1-, 2- , 3- and 5-year survival rates were 87.3%, 81.5%, 74.3%, and 65.3%, respectively. In general, 54 (56%) of the patients had NLR ≤3, while 43 (44%) had NLR >3. Mean survival times were 169.72±14.2 (95%CI 141.86-197.56) and 133.88±18.95 (95%CI 96.72-171.03) months for NLR ≤3 and NLR >3 patients, respectively. Median survival time was 223 months for NLR ≤3 patients, whereas it was 118±66.11 (95%CI 0-247.58) for >3 patients. The 1-, 2-, 3- and 5- year survival rates were 92.6%, 86.4%, 82% and 72.3% for NLR ≤3 and 80.3%, 75.6%, 65% and 56.8% for NLR >3 patients, respectively, indicating statistical significance (p=0.047).

Conclusion: In NPC, a pre-treatment NLR above three indicates an unfavorable prognosis in survival and may be a valuable prognostic biomarker. A large-scale prospective study is necessary to validate the prognostic significance of NLR in NPC patients and to determine precise cut-off values.

Keywords: nasopharyngeal carcinoma, neutrophil-to-lymphocyte ratio, survival

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Received: 13.01.2024 **Accepted:** 19.03.2024 **Published:** 31.01.2025

INTRODUCTION

Nasopharyngeal cancer (NFC) is a malignant tumor developing in the nasopharyngeal region. This area is located at the back of the nasal cavity and NFC is a rare type of cancer worldwide (1). However, it is more common in Asia and Southeast Asia. Especially in China, the incidence is as high as 80 per 100,000 person-years (2,3).

Diagnosis of NFC involves various methods, such as imaging tests and tissue biopsy, as well as symptoms and physical examination. Symptoms include prolonged nasal congestion, nosebleeds, difficulty swallowing, earache, and voice changes. During a physical exam, an endoscopy may be performed to examine the back of the throat. Imaging tests such as magnetic resonance imaging (MRI) and computed tomography (CT) are used. Tissue biopsy provides a definitive diagnosis of cancer cells and helps to determine the stage of the tumor (4,5).

Treatment of NFC depends on the stage of the tumor, the patient's overall health, and other factors. Treatment options include radiotherapy (RT) and chemoradiotherapy (CRT). T1 tumor detected at an early stage can only be treated with radiotherapy, while other stages can be treated with chemoradiotherapy. The most common form of treatment for NPC is radiotherapy, with 5-year overall survival (OS) rates ranging from 66% to 70% (6). However, the long-term survival of many patients remains poor due to high rates of distant metastasis and local recurrence after radiation (7,8).

The prognosis of NFC varies based on staging, response to treatment, and other factors. Patients diagnosed at the early stages usually have a better prognosis. However, patients diagnosed in advanced stages may have a poorer prognosis. Post-treatment follow-up includes regular evaluation of the patients' health and ensures early detection of possible recurrence or complications. However, these factors alone are not always sufficient for accurate prognostic predictions. Therefore, it is essential to identify biomarkers that are accurate and easy to use to for improving prognostic evaluations in NPC patients.

Evidence suggests that proinflammatory tumor microenvironments are closely linked to the occurrence and spread of cancer. While neutrophils are inflammatory cells that have an impact on the immune system's cytotoxic activity, lymphocytes are immune cells that have an anticancer effect. The neutrophil-to-lymphocyte ratio (NLR) serves as a key biomarker indicative of systemic inflammation. As a biomarker, NLR has been shown to improve prognostic evaluations in vairous malignancies, such as breast cancer, gastric neuroendocrine neoplasms, esophageal squamous cell carcinoma, and non-small cell lung cancer (9). An increased NLR, along with elevated neutrophil levels and/or reduced lymphocyte levels, serves as a biomarker reflecting the imbalance between pro- and antitumor immune activity in the host. Additionally, NLR can be easily derived from complete blood count results, making it a potential prognostic biomarker for NPC. Several studies have already explored the relationship between pretreatment NLR and NPC characteristics, as well as its prognostic significance in NPC patients. NLR has several suggested cutoff values (ranging from 2.28-3.00, with a median of 2.32), but the research indicates that, regardless of the cutoff value, NLR is a reliable predictive marker (9). However, the findings of these investigations have been proven contradictory.

In this study, we aim to evaluate the effect of neutrophil-lymphocyte ratio (NLR) on survival in NFC to enable a more accurate assessment of pre-treatment NLR as a predictive biomarker for patients with NPC, in light of its potential prognostic utility.

MATERIALS AND METHODS

Patient selection

We retrospectively reviewed all patients who received NPC treatment at our facility between 1998 and 2022. Patients with metastatic disease and prior or ongoing cancers were excluded from the study. The study population comprised 150 NPC patients with histological diagnoses and curative care between January 1998 and December 2022. This retrospective study was approved by the Ethics Committee (Project No. 2017-77, Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee).

Prior to therapy, all patients underwent a customary thorough physical examination. Biochemical assays and a complete blood counts were assessed. Routine clinical staging and imaging, such as computed tomography of the thorax and MRI scans of the head and neck, were carried out. Some patients were eligible for whole-body fludoxyglucose F 18 (18 F-FDG) positron emission tomography (PET)-CT imaging. The patients were staged according to the American Joint Committee on Cancer (AJCC).

Patients and treatment

Patients with T1N0M0 were treated with radiotherapy (RT) alone, while those with T2 or N1, M0 received chemoradiotherapy (CRT). The three cycles of cisplatin 100 mg/m2 (days 1, 21, and 42) or 40 mg/m2 weekly were employed as the chemotherapeutic dosage. Between 1998 and 2010, the 2D-RT technique was used, while the Intensity-Modulated Radiation Therapy (IMRT) technique was adopted from 2010 to 2022.

Radiotherapy area

Primary tumor and positive lymph nodes were included in the RT region. A margin of 5–10 mm was given around the area, with a 1 mm margin allowed for the brainstem, spinal cord, optic nerve, and chiasm, and 70 Gy RT is administered in 2Gy fractions. The entire nasopharynx, the clivus, the base of the skull, the pterygoid fossa, the parapharyngeal space, the sphenoid sinus, posterior ethmoid sinuses, posterior maxillary sinuses, and the posterior third of the nasal cavity level 1b- for N+ disease in both bilateral cervical lymph nodes, 4, skip level 1b for N0 disease, and 2Gy to 60 Gy RT was given to the retropharyngeal lymph nodes.

Follow-up

Follow-up visits were scheduled every three months for the first three years and every six months for the subsequent three years. To confirm locoregional insufficiency or distant metastases, fine-needle aspiration or biopsy was performed. Each visit included a thorough physical examination, repeat complete blood count, biochemical testing, brain and neck MRI, a thorax and abdomen computed tomography, and any other clinically indicated procedures. Follow-up continued from the initial diagnosis until the last visit or the date of death.

Statistical analysis

Statistical analysis of the collected data was performed using IBM SPSS Statistics 23. Time to local recurrence, regional recurrence, metastatic development, or death after RT or CRT were considered clinical outcomes. OS and disease-free survival rates (DFS) were calculated using the Kaplan-Meier technique. To examine differences between subgroups and identify variables having independent prognostic relevance on survival, a bilateral log-rank test was utilized. A p-value of 0.05 was used as the threshold for statistical significance in all tests

RESULTS

Patient characteristics

A total of 97 patients, who were treated for NPC between 1998 and 2022 and had available data, were included in the study. NLR was ≤3 in 54 (56%) and 43 (44%) NLR >3. The mean age of the patients was 49.64±14.51 (range: 12-82) years. Four patients were ≤18 years old and 93 patients were >19 years old. Sixty-three (65%) patients were male, 34 (35%) patients were female. NLR was ≤3 in 38 (39%) of male patients and >3 in 25 (26%). NLR was ≤3 in 16 (16%) of female patients and >3 in 18 (19%).

Ebstein Barr Virus (EBV) was negative in 3 (3%) patients (1 (1%) with NLR ≤3 and 2 (2%) with NLR >3). EBV was positive in 25 (26%) patients (17 (18%) with NLR ≤3 and 8 (8%) with NLR >3). EBV status was unknown in 69 (71%) patients (36 (37%) with NLR ≤3 and 33 (34%) with NLR >3).

Histology was unknown in 8 (8%) patients, 6 (6%) patients type I (keratinized squamous cell carcinoma), 10 (10%) patients type IIA (Non- keratinized squamous cell carcinoma, no lymphoid infiltration), and 73 (76%) patients were type IIB (Non- keratinized squamous cell carcinoma, lymphoid infiltration is present). In 2 (2%) patients whose histology was unknown, NLR was ≤3 and 6 (6%) NLR was >3. NLR was ≤3 in 1 (1%) type I patients and NLR was >3 in 5 (5%) patients. NLR was

≤3 in 5 (5%) type IIA patients and NLR was >3 in 5 (5%) patients. NLR was ≤3 in 46 (48%) type IIB patients and NLR was >3 in 27 (28%).

29 (30%) patients were T1, 27 (28%) patients were T2, 22 (23%) patients were T3 and 19 (19%) patients were T4. 17 (17%) patients had N0, 18 (19%) patients had N1, 58 (60%) patients had N2 and 4 (4%) patients had N3. 1 (1%) patient was M1. According to the stages; 4 (4%) patients were stage I, 18 (19%) patients were stage II, 54 (56%) patients were stage III, 20 (20%) patients were stage IVA, and 1 (1%) patient was stage IVB. NLR was ≤3 in 2 (2%) of stage I patients and NLR was >3 in 2 (2%) patients. NLR was ≤3 in 10 (11%) of stage II patients and NLR was >3 in 8 (8%) patients. NLR was ≤3 in 29 (30%) of stage III patients and NLR was >3 in 25 (26%) patients. NLR was ≤3 in 12 (12%) of stage IVA patients and NLR was >3 in 8 (8%) patients. NLR was >3 in stage IVB 1 (1%) patient. Patient characteristics are shown in Table 1.

Table 1. Patient characteristics according to NLR

		N (%)	NRL N (%)	
			≤3	>3
Age	≤18	4 (4%)	3 (3%)	1(1%)
	>19	93 (96%)	51 (53%)	42 (44%)
Sex	Male	63 (65%)	38 (39%)	25 (26%)
	Female	34 (35%)	16 (16%)	18 (19%)
T	1	29 (30%)	22 (23%)	7 (7%)
	2	27 (28%)	14 (15%)	13 (13%)
	3	22 (23%)	7 (7%)	15 (16%)
	4	19 (19%)	12 (12%)	7 (7%)
N	0	17 (17%)	8 (8%)	9 (9%)
	1	18 (19%)	10 (11%)	8 (8%)
	2	58 (60%)	34 (35%)	24 (25%)
	3	4 (4%)	2 (2%)	2 (2%)
M	0	96 (99%)	55 (57%)	41 (42%)
	1	1 (1%)	0 (0%)	1 (1%)
Stage	I	4 (4%)	2 (2%)	2 (2%)
	II	18 (19%)	10 (11%)	8 (8%)
	III	54 (56%)	29 (30%)	25 (26%)
	IVA	20 (20%)	12 (12%)	8 (8%)
	IVB	1 (1%)	0 (0%)	1 (1%)
Histology	I	6 (6%)	1 (1%)	5 (5%)
	IIA	10 (10%)	5 (5%)	5 (5%)
	IIB	73 (76%)	46 (48%)	27 (28%)
	Unknown	8 (8%)	2 (2%)	6 (6%)
EBV	Negative	3 (3%)	1 (1%)	2 (2%)
	Positive	25 (26%)	17 (18%)	8 (8%)
	Unknown	69 (71%)	36 (37%)	33 (34%)

t: tumor stage, n: nodal stage, m: methastasis, NLR: neutrophil to lymphocyte ratio, EBV: Ebstein-Barr Virus.

Survival

The follow-up period was 79.4±72.1 (2-279) months. The mean OS of all patients was 159.37±13.66 (132.97-185.76) months, with a median of 205±31.11 (144-265.99) months. The 1-, 2-, 3- and 5-year survival rates were 87.3%, 81.5%, 74.3%, and 65.3%, respectively (Figure 1).

Neutrophil-to-lymphocyte ratio (NLR)

NLR was calculated by the neutrophil and lymphocyte measurements of the patients before radiotherapy/chemoradiotherapy. NLR cut-off value was accepted as 3 and patients were divided into two groups (≤3 and >3).

In total, 54 (56%) of patients had NLR ≤3, while 43 (44%) had NLR >3. The mean survival times were 169.72±14.2 (95%CI 141.86-197.56) and 133.88±18.95 (95%CI 96.72-171.03) months for NLR ≤3 and NLR >3 patients, respectively. The median survival time was 223 months for NLR ≤3 patients, whereas it was 118±66.11 (95%CI 0-247.58) for >3 patients. The 1-, 2-, 3- and 5-year survival rates were 92.6%, 86.4%, 82% and 72.3% for NLR ≤3 and 80.3%, 75.6%, 65% and 56.8% for NLR >3 patients, respectively, indicating statistical significance (p=0.047) (Figure 2).

Three (3%) of patients aged ≤18 years had NLR ≤3 and the 1-, 2-, 3- and 5-year survival rates were 100%, 100%, 100% and 100%. There was 1 (1%) patient with NLR >3 and did not survive beyond a year. There was no statistical difference between the two groups

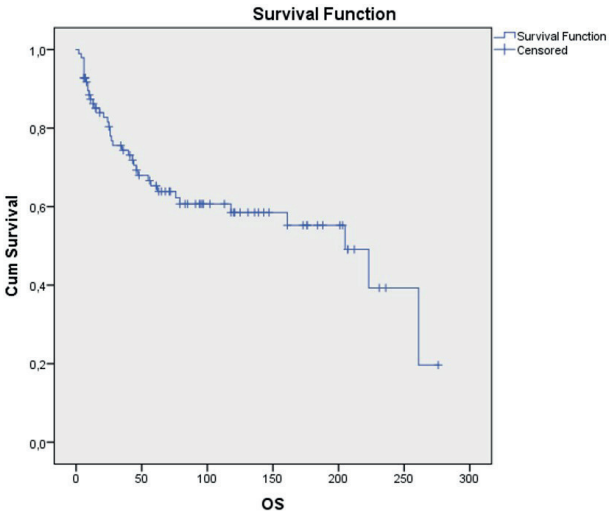

Figure 1. Overall survival.

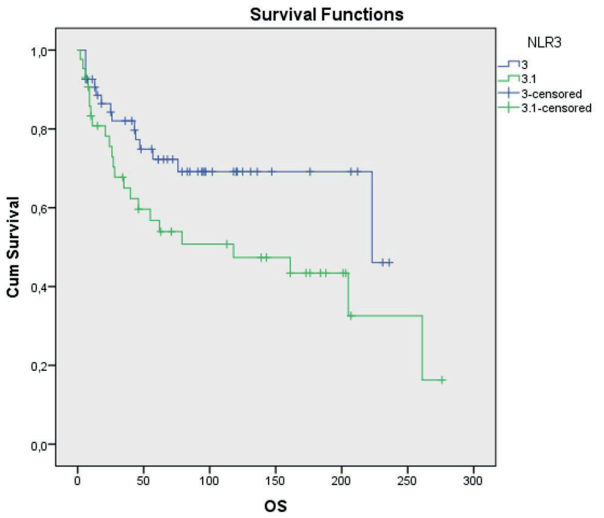

Figure 2. Overall survival by NLR.

according to age (p=0.157). Among patients aged >19 years, 51 (53%) patients had NLR ≤3 and 42 (44%) had NLR >3. The mean survival time was 166.94±14.66 (95%CI 138.2-195.68) and 137±19.17 (95%CI 99.43) -174.58) months, the median survival time was 223 and 118.77.63±36.37 (0-270.16) months. The 1-, 2-, 3- and 5-year survival rates were 92.2%, 85.7%, 81.1% and 70.9% for NLR ≤3 and 82.8%, 77.5%, 66.7% and 58.2% for NLR >3, respectively. This difference was not statistically significant (p=0.088).

Among male patients, 38 (39%) had NLR ≤3 and 25 (26%) had NLR >3. The mean survival time was 165.13±16.64 (95%CI 132.51-197.75) and 119.9±24.88 (95%CI 71.11-1186.68) months, median survival time was 223±105.56 (95%CI 16.09-429.9) and 62±36.37 (0-133.29) months. The 1-, 2-, 3- and 5-year survival rates were 89.5%, 83.6%, 80.4% and 73% for NLR ≤3 and 70.3%, 65.9%, 57.1% and 47.6% for NLR >3, respectively. This difference was not statistically significant (p=0.061). Among female patients, 16 (16%) had NLR ≤3 and 18 (19%) had NLR >3. The mean survival time was 175.07±25.62 (95%CI 124.84-225.29) and 159.08±28.81 (95%CI 102.6-215.57) months, the median survival time of NLR >3 patients was 205±81.82 (95%CI 44.63-365.37) months. The 1-, 2-, 3- and 5-year survival rates were 100%, 85.7%, 77.9% and 70.1% for NLR ≤3 and 94.4%, 81.9%, 75.5% and 63% for NLR >3, respectively. This difference was not statistically significant (p=0.355).

When the patients were evaluated according to EBV; 1 (1%) of EBV negative patients had an NLR ≤3, and 2 (2%) patients with NLR>3 had a1-, 2-, 3- and 5-year survival rate of 50%, and this difference shows no statistical significance (p=0.480). 17 (18%) of EBV positive patients had NLR ≤3 and 8 (8%) patients had NLR>3. The mean survival time was 69.36±9.03 (95%CI 51.66-87.07) and 60.66±9.43 (95%CI 42.17-79.15) months; the 1-, 2-, 3- and 5-year survival rates were 88.2%, 79.4%, 69.5% and 69.5% for NLR ≤3 and 83.3%, 83.3%, 83.3% and 83.3% for NLR >3, respectively. This difference was not statistically significant (p=0.636). In patients with unknown EBV, 36 (37%) has been NLR ≤3 and 33 (34%) NLR >3, mean survival time was 176.99±15.91 (95%CI 145.81-208.18) and 129.49±19.88 (95%CI 90.51) -168.48) months, median survival time was 223 and 79±62.16 (95%CI 0-200.84) months; the 1-, 2-, 3- and 5-year survival rates were 94.4%, 85.9%, 82.9% and 73.3% for NLR ≤3 and 81.8%, 75.8%, 63.6% and 51.5% for NLR >3, respectively. This difference was not statistically significant (p=0.026).

When the patients were evaluated according to histology; 1 (1%) of type I patients had NLR ≤3 and 5 (5%) NLR > 3, the mean survival time was 6 and 62.2±27.28 (95%CI 8.71-115.68) months; median survival time was 6 and 35±7.66 (95%CI 19.97-50.03) months;1, 2, 3 and 5 year survival rates were 80%, 40% and 40% for NLR >3 respectively. There were no NLR ≤3 patients

surviving 1 year. This difference was statistically significant (p=0.025). Type IIA patients had 5 (5%) NLR ≤3 and 5 (5%) NLR > 3, the mean survival time was 179.5±44.6 (95%CI 92.08-266.91) and 32.13±9.68 (95%CI 13.15-51.11) months respectively. The 1-, 2-, 3- and 5- year survival rates were 100%, 100%, 75% and 75% for NLR ≤3 and 80%, 80%, 53%- and 54-years survival rates for NLR >3, respectively. This difference was not statistically significant (p=0.171). Type IIB patients had 46 (48%) NLR ≤3 and 27 (28%) NLR > 3, the mean survival time was 171.55±15.65 (95%CI 70.86-202.23) and 169.75±23.7 (95%CI 123.29-216.21) months respectively. The median survival time was 205±57.36 (95%CI 92.57-317.42) months for NLR >3. The 1-, 2-, 3- and 5-year survival rates were 93.5%, 86.5%, 83.7% and 72% for NLR ≤3 and 88%, 79.6%, 71.2% and 66.8% for NLR >3, respectively, and this difference was not statistically significant (p=0.540). Of the patients whose histology was unknown, 2 (2%) NLR ≤3 and 6 (6%) NLR > 3, the mean survival time was 223 and 71.33±31.01 (95%CI 10.55-132.11) months respectively. The median survival time was 223 and 11±30 (95%CI 0-69.81) months. The 1-, 2-, 3- and 5-year survival rates were 100%, 100%, 100% and 100% for NLR ≤3 and 50%, 50%, 50% and 33.3% for NLR >3, respectively. This difference was not statistically significant (p=0.170). Survival according to patient characteristics is shown in Table 2.

According to stage, there were 2 (2%) NLR ≤3 and 2 (2%) NLR >3 Stage I patients, mean survival time was 14±2.82 (95%CI 8.45-19.54) and 10 months; median survival time was 10 and 10 months; the 1-, 2-, 3- and 5-year survival rates were 50%, 50%, 50% and 50% for NLR ≤3 and 50%, 50%, 50% and 50% for NLR >3, respectively, and this difference was not statistically significant (p=0.317). There were 10 (10%) NLR ≤3 and 8 (8%) NLR >3 Stage II patients, mean survival time was 186.62±19.05 (95%CI 149.26-223.98) and 212.57±37.94 (95%CI 138.2-286.93) months; the 1-, 2-, 3- and 5-year survival rates were 100%, 100%, 100% and 87.5%for NLR ≤3 and 100%, 100%, 100% and 85.7% for NLR >3, respectively, and this difference was not statistically significant (p=0.538). There were 29 (30%) NLR ≤3 and 25 (26%) NLR >3 Stage III patients, mean survival time was 158.86±20.54 (95%CI 118.58-199.15) and 141.55±25.58 (95%CI 91.4-191.7) months; the 1-, 2-, 3- and 5-year survival rates were 92.9%, 84.6%, 80.4% and 67.2%for NLR ≤3 and 87.1%, 82.3%, 67.4% and 62.2% for NLR >3, respectively, and this difference was not statistically significant (p=0.403). There were 12 (13%) NLR ≤3 and 8 (8%) NLR >3 Stage IVA patients, mean survival time was 141.92±35.77 (95%CI 71.81-212.03) and 80.37±26.88 (95%CI 27.67-133.07) months; median survival time was 223 (95%CI 12.94-30.85) and 28±24.04 (95%CI 0-75.12) months; the 1-, 2-, 3- and 5-year survival rates were 81.8%, 71.6%, 61.4% and 61.4% for NLR ≤3 and 75%, 62.5%, 50% and 37.5% for NLR >3, respectively, and this difference was not statistically significant (p=0.340). There were stage IVB 1 (1%) patient with NLR >3 and the mean survival time was 3 months. Survival by stage and NLR characteristics are shown in Table 3.

DISCUSSION

The TNM staging system for NPC is the primary model used for predicting survival outcomes (9). However, it does not consider the tumor's inherent biological variability. In this study, we aimed to investigate the relationship between NLR rate and OS to predict overall survival in nasopharyngeal carcinoma. We included age, stage, EBV status, and histology in the nomogram for OS.

Recent studies have indicated that EBV DNA levels in plasma, serum, or peripheral blood cells serve as a valuable prognostic marker for NPC patients (10). However, routine EBV DNA testing has only recently been implemented in our clinic. In addition, EBV DNA testing procedures may vary between clinics. Therefore, the prognostic significance of NLR in OS could not be demonstrated in a small number of patients who underwent EBV testing in our study.

Recent research highlights the pivotal role of inflammation in tumor pathogenesis, with proinflammatory tumor microenvironments closely linked to cancer progression (9). Neutrophils and lymphocytes are key indicators of systemic inflammation and immune status. A higher NLR signifies an increase in neutrophils and/or a reduction in lymphocytes. Lymphocytes generally have antitumor functions, while neutrophils are associated with inflammation and may impair the cytolytic

Table 2. Overall Survival by patient and NLR characteristics

		NLR	n (%)	Mean (95% CI)	Median (95% CI)	1 y (%)	2 y (%)	3 y (%)	5 y (%)	p
General		≤3	54 (56%)	169.72±14.2 141.86-197.56	223	92.6	86.4	82	72.3	0.047
		>3	43 (44%)	133.88±18.95 96.72-171.03	118±66.11 0-247.58	80.3	75.6	65	56.8	
Age	≤18	≤3	3 (3%)	-	-	100	100	100	100	0.157
		>3	1 (1%)	10	10	0	0	0	0	
	>19	≤3	51 (53%)	166.94±14.66 138.2-195.68	223	92.2	85.7	81.1	70.9	0.088
		>3	42 (44%)	137±19.17 99.43-174.58	118±77.63 0-270.16	82.8	77.5	66.7	58.2	
Sex	Male	≤3	38 (39%)	165.13±16.64 132.51-197.75	223±105.56 16.09-429.9	89.5	83.6	80.4	73	0.061
		>3	25 (26%)	119.9±24.88 71.11-168.68	62±36.37 0-133.29	70.3	65.9	57.1	47.6	
	Female	≤3	16 (16%)	175.07±25.62 124.84-225.29		100	85.7	77.9	70.1	0.355
		>3	18 (19%)	159.08±28.81 102.6-215.57	205±81.82 44.63-365.37	94.4	81.9	75.5	63	
EBV	Negative	≤3	1 (1%)	-	-	-	-	-	-	0.480
		>3	2 (2%)	-	-	50	50	50	50	
	Positive	≤3	17 (18%)	69.36±9.03 51.66-87.07	-	88.2	79.4	69.5	69.5	0.636
		>3	8 (8%)	60.66±9.43 42.17-79.15	-	83.3	83.3	83.3	83.3	
	Unknown	≤3	36 (37%)	176.99±15.91 145.81-208.18	223	94.4	85.9	82.9	73.3	0.026
		>3	33 (34%)	129.49±19.88 90.51-168.48	79±62.16 0-200.84	81.8	75.8	63.6	51.5	
Histology	I	≤3	1 (1%)	6	6	0	-	-	-	0.025
		>3	5 (5%)	62.2±27.28 8.71-115.68	35±7.66 19.97-50.03	80	80	40	40	
	IIA	≤3	5 (5%)	179.5±44.6 92.08-266.91		100	100	75	75	0.171
		>3	5 (5%)	32.13±9.68 13.15-51.11	46	80	80	53	0	
	IIB	≤3	46 (48%)	171.55±15.65 70.86-202.23		93.5	86.5	83.7	72	0.540
		>3	27 (28%)	169.75±23.7 123.29-216.21	205±57.36 92.57-317.42	88	79.6	71.2	66.8	
	Unknown	≤3	2 (2%)	223	223	100	100	100	100	0.170
		>3	6 (6%)	71.33±31.01 10.55-132.11	11±30 0-69.81	50	50	50	33.3	

EBV: Ebstein-Barr Virus, NLR: neutrophil to lymphocyte ratio.

Table 3. Overall Survival by stage and NLR characteristics

		NLR	N (%)	Mean (95% CI)	Median (95% CI)	1 y (%)	2 y (%)	3 y (%)	5 y (%)	p
Stage	I	≤3	2 (2%)	14±2.82 8.45-19.54	10	50	50	50	50	0.317
		>3	2 (2%)	10 10-10	10	50	50	50	50	
	II	≤3	10 (10%)	186.62±19.05 149.26-223.98	-	100	100	100	87.5	0.538
		>3	8 (8%)	212.57±37.94 138.2-286.93	-	100	100	100	85.7	
	III	≤3	29 (30%)	158.86±20.54 118.58-199.15	-	92.9	84.6	80.4	67.2	0.403
		>3	25 (26%)	141.55±25.58 91.4-191.7	118±64.1 0-243.64	87.1	82.3	67.4	62.2	
	IVA	≤3	12 (13%)	141.92±35.77 71.81-212.03	223	81.8	71.6	61.4	61.4	0.340
		>3	8 (8%)	80.37±26.88 27.67-133.07	28±24.04 0-75.12	75	62.5	50	37.5	
	IVB	≤3	0 (0%)	-	-	-	-	-	-	
		>3	1 (1%)	4	4	0	-	-	-	

NLR: neutrophil to lymphocyte ratio.

activity of lymphocytes and natural killer cells. Tumor growth is believed to be suppressed when a substantial infiltration of neutrophils occurs within the tumor microenvironment (9). Therefore, NLR acts as a biomarker that reflects the imbalance between pro- and anti-tumor activities within the inflammatory response.

Compared to other prognostic biomarkers, NLR stands out due to its simplicity and affordability (9). As a routine test that incurs no additional costs for patients, it is particularly appealing as a prognostic marker for NPC in clinical practice. Furthermore, NLR has been shown to have prognostic value in various cancers, including pancreatic tumors (11), brain tumors (12), gastric neuroendocrine neoplasms (13), esophageal squamous cell carcinoma (14), non-small cell lung cancer (15), and breast cancer (16).

However, the practical application of NLR, especially in NPC patients, needs to be better defined. Sun et al. demonstrated that an NLR ≥2.7 was significantly correlated with progression-free survival (17). Conversely, Chua et al. found that an NLR ≥3.0 did not serve as a prognostic factor in their randomized controlled trial (18). Jin et al. reported that an NLR of 3.6 was associated with survival in patients with metastatic NPC (19). Pan et al. identified an NLR cut-off of 2.92 for overall survival in stage II NPC patients, noting it as an independent prognostic factor (10). In our study, we used an NLR cut-off of 3 for overall survival in NPC patients. Aligned with prior findings in other cancer types, our study indicates that pre-treatment NLR holds significant potential as a prognostic biomarker for NPC, with higher pre-treatment NLR levels possibly acting as a prognostic marker in various cancers (9).

This study has several limitations. First, it is a retrospective study. Second, it covers a long period of time, and our patient group is heterogeneous.

CONCLUSION

In NPC, NLR above three before treatment suggests that it may suggest an unfavorable prognosis in survival and may be a valuable prognostic biomarker. A large-scale prospective study is necessary to validate

the prognostic significance of NLR in NPC patients and to determine precise cut-off values.

Ethical approval

This study has been approved by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval date 15/05/2017, number 2017/77). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: HBÇ; Concept: MK; Data collection or Processing: MK, AB, HBÇ; Analysis or Interpretation: MK; Literature search: MK, AB; Writing: MK, AB, HBÇ. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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NORTHWESTERN MEDICAL JOURNAL

Northwestern Med J. 2025;5(1):25-32
DOI: 10.54307/NWMJ.2025.76

RESEARCH ARTICLE

The evaluation of the malnutrition in hospitalized infants

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Cite as: Akbay Ak S, Baltalı O, İlhan Ö, Akman S. The evaluation of the malnutrition in hospitalized infants. Northwestern Med J. 2025;5(1):25-32.

ABSTRACT

Aim: Malnutrition is a state of inadequate nutrition that can be prevented or treated with appropriate nutrition. The aim of this study is to determine the nutritional status of hospitalized infants and to establish the relationship between anthropometric measurements and malnutrition with underlying acute or chronic diseases.

Materials and Methods: This study was cross-sectional, descriptive, and noninvasive. It included the infants who were hospitalized at the tertiary hospital between 2010 and 2012. Demographic data was collected through face-to-face interviews. Body mass index (BMI), BMI standard deviation score (SDS), BMI percentiles, SDS of body weight and height were calculated using the KIGS (Pfizer International Growth Database) Auxology calculator program.

Results: A total of 298 infants were included in the study. The mean age of them was 7.18 ± 4.8 months and 185 children (62.1%) were male. At the time of hospitalization, 101 (33.9%) patients had chronic disease. Neurological diseases were the most common chronic diseases, accounting for 31.7% (n=32) of the chronic diseases. As the severity of malnutrition increased, the likelihood of accompanying chronic illness increased ($p<0.05$). In the presence of chronic disease, anthropometric measurements of infants were significantly lower ($p<0.05$). There were significant correlations between the presence of chronic illness, lenght of hospitalization, relative weight, and BMI percentiles ($p <0.05$).

Conclusion: Mild and moderate malnutrition was detected even in patients who were admitted with acute illness and were not accompanied by chronic disease. Early diagnosis and treatment of nutritional disorders can be important in reducing mortality and morbidity. The aim of the treatment of malnutrition detected during hospitalization should provide better recovery and improvement, increase the quality of life, and raise healthy individuals.

Keywords: chronic disease, hospitalization, infant, malnutrition

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Received: 09.01.2024 **Accepted:** 23.09.2024 **Published:** 31.01.2025

INTRODUCTION

Malnutrition is a state of inadequate nutrition that can be prevented or treated with appropriate nutrition (1,2). Especially in underdeveloped and developing countries, it remains a serious public health problem. Since infancy is a period of rapid growth and development, nutritional problems can easily lead to both malnutrition and health problems in the child's future life (1-3). In the evaluation of nutritional status and degree of malnutrition, in addition to history and physical examination findings, children's height, body weight, and body mass index (BMI) measurements are compared with normal values of the same age group. Anthropometric assessment, especially in early childhood, allows early diagnosis of malnutrition and is useful for long-term follow-up (1,2,4). This study aimed to investigate the relationship between malnutrition in hospitalized infants and the sociodemographic characteristics of their parents, the presence of underlying acute or chronic diseases and anthropometric measurements.

MATERIALS AND METHODS

This study is cross-sectional descriptive and noninvasive. It was planned to include infants who were hospitalized at a tertiary hospital between 2010 and 2012. The mothers were informed about the study and then the study was administered to children and their mothers who agreed to participate. The infants whose parents didn't give their consent and those with missing records were excluded. The remaining 298 infants were included in the study. The purpose of the study was to evaluate malnutrition in the hospitalized infants.

The study was approved by the Clinical Research Ethics Committee of İzmir Tepecik Training and Research Hospital (No: 2010/2;6), and all procedures were performed in accordance with the Declaration of Helsinki and with the ethical standarts of the national research committee.

The number of hospitalizations, birth weight, duration of breastfeeding, presence of underlying diseases were noted in a face to face interview. The cases with more than one hospitalization were included in the study once. Premature babies were evaluated according to the corrected age. The birth weights of the cases below the 10th, between the 10-90th percentile and above the 90th percentile of gestational age (GA) were classified as small for GA (SGA), appropriate for GA (AGA) and large for GA (LGA), respectively. At the time of the survey, the current duration of breastfeeding (in months) was recorded. Patients who exclusively breastfed for the first six months and were only breastfed for less than six months were classified as sufficient, and those only received human milk for less than six months were classified as insufficient. The timing of the introduction of complementary nutrition was categorized as early, on time, or late, based on whether it began before, at, or after six months, respectively. Anthropometric measurements were recorded in accordance with a healthy child follow-up protocol. Weight was measured with an electronic weighing machine with a sensitivity range of 0.01kg, height was measured with a portable height scale. Relative weight was calculated by dividing of the measured weight of the infant to its ideal weight (the weight of a healthy child with the same height). Also, BMI, BMI standard deviation score (SDS), BMI percentiles, SDS of body weight and height were calculated using the KIGS (Pfizer International Growth Database) Auxology calculator program. A tool called "Holtain skinfold caliper" was used to evaluate subcutaneous fat tissue and triceps skin thickness was measured at the triceps region of the left arm. The middle limb was measured with the standard tape on the middle of the left arm. Acute and chronic diseases were classified as respiratory system diseases, cystic fibrosis, urogenital system diseases, gastrointestinal system (GIS) diseases, neurological diseases, motor mental retardation, heart diseases, infectious diseases, connective tissue diseases, metabolic diseases, hematological diseases, immunodeficiency and dermatological diseases, and diseases not included in this category were grouped as 'other'.

The data obtained in the study were recorded in Statistical Package for Social Sciences (SPSS) for Windows 20.0 program for statistical analysis. Demographic and socio-demographic characteristics of children and their families were evaluated by frequency analysis. Chi-square and T-test were used for the comparative statistics. The results were evaluated as 95% confidence interval, $p<0.05$ was statistically significant.

RESULTS

The mean age of the 298 patients aged 1-24 months was 7.18 ± 4.8 months (median=6 months). Of these, 185 children (62.1%) were male; 152 (51%) children were between 1-6 months old, 108 (36.2%) were between 7-12 months old, and 38 (12.8%) were between 13-24 months old. Twenty six (8.7%) cases were SGA. The median lenght of hospital stay was nine days (1-139 days). The median number of previous hospitalizations and siblings of the patients were two (1-12), one (1-7), respectively. Considering the educational status of the family members; 35 (11.7%) mothers and 12 (4%) fathers were illiterate, 189 (63.4%) mothers and 196 (65.8%) fathers had only primary school education.

The median duration of breastfeeding was 4 months, and the median duration of exclusive breastfeeding was 2.5 months. However, the age at the time of the study was indicated as the time of the intake of breast milk, so this information cannot give us a definite judgment as the duration of breastfeeding for the whole patient group. The patients who were breastfed exclusively for less than six months were termed as insufficient were 57.4% of the cases. The number of patients receiving the complementary nutrition was 241; 57.4% of these patients started early. The median at which cow milk was introduced was 9.5 months. Besides, 24 patients (8.1%) were using enteral feeding tubes because of underlying diseases. During the study, 180 patients were between 4-12 months old and only 56.7% (102) of them were receiving iron supplements.

At the time of hospitalization, 101 (33.9%) patients had chronic diseases. Neurological diseases were the most common, accounting for 31.7% (n=32) of all chronic diseases and GIS was the second most common system with chronic diseases (18.8%).

Infants who were exclusively breastfed had statistically higher BMI percentiles and relative weight and fewer hospitalizations than patients who were not breastfed sufficiently ($p<0.05$). Patients with BMI below 5th percentile, between 5th and 85th percentiles, and above 85th percentile were grouped as underweight, normal weight, and overweight, and their percentiles were 19.8%, 61.4% and 18.8%; respectively. The relative weights of 54.7% (163) of the patients were between 90%-110% and were evaluated as normal. There was a positive correlation between relative weight and triceps thickness, arm circumference. The thickness of the triceps and the arm circumference decreased, as the relative weight decreased [Pearson correlation coefficient, $r=0.376$ (CI 0.23-0.52) and $r=0.37$ (CI:0.23-0.51)] ($p<0.001$ and $p<0.001$).

The infants were grouped according to their acute illnesses at the time of admission. The most common was respiratory system diseases with 54.7% (n=163), while infectious diseases were the second (n=69, 23.2%). Severe, moderate and mild malnutrition according to relative weight were observed in 6.9% (n=7), 14.9% (n=15) and 29.7% (n=30) of the cases with chronic diseases, respectively. Severe, moderate and mild malnutrition by relative weight were found in 1% (n=2), 3% (n=6) and 17.3% (n=34) of the cases without chronic diseases, respectively. As the severity of malnutrition increased, the likelihood of accompanying chronic disease increased ($p<0.05$). In the group of patients with chronic disease, 25% of the cases with nutritional deficiency (having less than 90% of relative weight) were diagnosed with neurological disease and 21.2% of them had heart diseases, and there was a significant correlation between type of chronic disease and relative weight ($p<0.05$) (Table 1).

Infants with chronic diseases were most frequently hospitalized with respiratory system diseases (40.6%). Infectious diseases were the second most common cause of admission (21.8%). It was found that infants with body mass index (BMI) less than the 5th percentile and chronic diseases were most frequently hospitalized due to infectious and respiratory diseases (41.5% and 29.3%; respectively). In the presence of chronic disease, anthropometric measurements of cases were found to be significantly lower ($p<0.05$) (Table 2).

Table 1. Comparison of relative weight and type of chronic diseases

	Relative weight		
	<%90 n (%)	**%90-110 n (%)**	**>%110 n (%)**
Neurological diseases	13 (%25)	17 (%42.5)	2 (%22.2)
GIS[1] diseases	7 (%13.5)	9 (%22.5)	3 (%33.3)
Heart diseases	11 (%21.2)	5 (%12.5)	0 (%0)
Others	7 (%13.5)	3 (%7.5)	1 (%11.1)
Cystic fibrosis	5 (%9.6)	1 (%2.5)	0 (%0)
Metabolic diseases	4 (%7.7)	1 (%2.5)	1 (%11.1)
Urogenital diseases	1 (%1.9)	2 (%5)	0 (%0)
Hematologic diseases	2 (%3.8)	1 (%2.5)	0 (%0)
Respiratory system diseases	1 (%1.9)	1 (%2.5)	0 (%0)
Chronic renal diseases	0 (%0)	0 (%0)	1 (%11.1)
Connective tissue diseases	0 (%0)	0 (%0)	1 (%11.1)
Immune deficiency	1 (%1.9)	0 (%0)	0 (%0)

[1]GIS: Gastrointestinal system

Table 2. Comparison of demographic findings with presence of chronic illness

	Chronic illness			
	Present	**Absent**	**p**	**CI %95**
Weight (kg)	6.07±2.22	7.55±2.23	**<0.001**	(-2.02)-(-0.95)
Height (cm)	62.77±9.02	66.27±8.45	**0.001**	(-5.58)-(-1.41)
BMI[1] (kg/m^2)	14.88±2.57	16.84±2.18	**<0001**	(-2.52)-(-1.40)
BMI SDS[2]	-1.35±1.88	0.31±1.59	**<0.001**	(-2.07)-(-1.25)
BM Percentile	25.34±31.74	55.84±33.00	**<0.001**	(-38.35)-(-22.66)
Weight for age (SDS)	-1.79±1.39	-0.23±1.21	**<0.001**	(-1.87)-(-1.26)
Height for age (SDS)	-1.64±2.02	-0.26±1.45	**<0.001**	(-1.78)-(-0.98)
Triceps thickness (cm)	8.85±2.77	11.45±2.15	**<0.001**	(-3.17)-(-2.03)
Arm circumference (cm)	11.76±2.18	13.44±1.69	**<0.001**	(-2.13)-(-1.23)
Relative weight	91.35±17.80	99.55±12.75	**<0.001**	(-11.72)-(-4.66)
Number of hospitalizations	2.89±1.98	1.61±0.87	**<0.001**	0.96-1.61
Lenght of hospitalization (day)	20.56±23.71	9.61±5.54	**<0.001**	7.46-14.45
Age (month)	7.54±4.64	6.99±4.87	0.347	(-0.60)-(1.71)
Birth weight (kg)	1.87±0.39	1.97±0.29	**0.011**	(-0.18)-(-0.02)

[1]BMI:body mass index, [2]SDS: standart deviation

While 37.9% (n=113) of the cases were hospitalized for more than 10 days, 54% (n=161) of the patients had been hospitalized before. A significant relationship was found between the lenght of hospitalization and the presence of chronic disease, relative weight and BMI percentiles ($p < 0.05$). The lenght of hospitalization was found to be significantly higher in patients with malnutrition ($p=0.013$). The number of hospitalizations was found to be significantly higher in those with chronic diseases, in the group with low relative weight and BMI percentiles, nutritional problems and low-income levels ($p<0.05$).

DISCUSSION

Healthy nutrition in childhood is defined as nutrition that meets all the energy and nutritional requirements necessary for the child to survive healthy and grow and develop (5). The World Health Organization (WHO) defines the protein energy malnutrition (PEM) as "a group of pathological syndromes, often associated with infections, most commonly seen in infants and young children and as a result of dietary deficiencies of protein and calorie" (2,6). Every year, 1-5% of children under the age of five worldwide die due to severe malnutrition (7). Recognition of cases with severe PEM is easy, but the detection and treatment of mild to moderate PEM are difficult to diagnose, the determination and resolution of their causes will reduce the morbidity and mortality, as well as the economic burden (8,9). In our study, malnutrition was detected in 31.5% of hospitalized infants.

Factors that play a role in the etiology of malnutrition are often based on the economic, psychosocial, and cultural factors (1,2). In a study conducted by Hendricks et al. in 2006 (10), it was reported that maternal education was the most important factor in the child's nutrition. According to data from the Turkish Population Health Surveys (TDHS) in 2008, 1/5 of the women were illiterate and hadn't completed primary school (11). Similarly, in our study, 19.8% of the mothers were non-literate and did not graduate from primary education. In addition, there was a negative correlation between family income and hospitalization.

The first two years of life are the period of most rapid growth and development, and proper nutrition during this period has important implications for older ages (12). The American Academy of Pediatrics (AAP) also recommends exclusive breastfeeding for the first six months of age (13). In the worldwide, exclusively breastfeeding rate of infants between 0 and 6 months of age is 34.8%, most of whom started complementary nutrition early (14). We found that the proportion of patients who received only breast milk for the first six months was 42.6%. The ratio of weight for height and BMI percentiles were found significantly higher and the number of hospitalizations were significantly lower in patients who were exclusively and sufficiently breastfed, compared to infants were not ($p<0.05$). The AAP issued a report in 2010 suggesting iron prophylaxis for term infants who were exclusively breastfed after four months of age (15). In our study, it was determined that 56.7% of the 180 patients between 4-12 months old were receiving iron prophylaxis. For this reason, we think that we have deficiencies in monitoring healthy children for iron supplementation.

Clinical findings as well as anthropometric measurements and biochemical parameters are used to evaluate nutritional status in children (4,16). Anthropometric methods frequently used in the evaluation of nutritional status include weight for age, height for age, BMI, relative weight, triceps thickness, and arm circumference. However, in 1990, Davies et al. (17) showed that subcutaneous thickness was poorly correlated with body fat mass at 5, 11, and 26 weeks of age. However, in our study, significant positive correlations were detected between relative weight and triceps thickness and arm circumference [Pearson correlation, $r=0.376$ (CI: 0.23-0.52) and $r=0.37$ (CI: 0.23-0.51)] ($p<0.001$ and $p<0.001$).

Nutritional deficiencies in the hospitalized children are particularly prevalent in children with chronic illnesses (18-20). In addition, immunodeficiencies can arise from nutritional deficiencies. For this reason, diseases are more severe and septicemia develops easily, further exacerbating malnutrition. Malnutrition has effects on mortality and morbidity. Therefore, patients with malnutrition should be monitored more carefully so

that these patients are likely to be hospitalized (9,19). In our study, 33.9% of the patients had chronic illnesses, 51.5% of them had malnutrition, and 6.9% of them had severe malnutrition based on the relative weight. In our patients without chronic diseases, the incidence of malnutrition was 21.3%, whereas the incidence of severe malnutrition was only 1%. It was found that the incidence of severe and moderate mulnutrition was increased in the presence of chronic diseases ($p<0.05$). In addition, anthropometric measurements of these patients were found to be significantly lower ($p<0.05$). Similarly, in the study by Doğan et al. (18), it was stated that nutritional deficiencies are more prevalent among those with chronic diseases and nutritional support was needed especially in patients with chronic renal failure, genetic disease, immunodeficiency and cystic fibrosis. In contrast, in our study, neurological diseases (31.7%) and GIS diseases (18.8%) were the most common chronic diseases among hospitalized infants. This difference may be due to the fact that our study group consisted of children aged 1–24 months, rather than the entire pediatric age group. In addition, in the group of patients with chronic diseases, 25% of the cases with nutritional deficiencies (less than 90% of relative weight) were diagnosed with neurological diseases and 21.2% of them had heart diseases, and there was a significant correlation between relative weight and type of chronic diseases ($p<0.05$). For this reason, we think that the increase in cases especially with chronic diseases such as neurological and cardiac diseases should be monitored more closely and nutritional support should be provided.

In a study conducted by Rocha et al. (21), the most common causes of death among children under five years of age hospitalized in Brazil were pneumonia (33%) and diarrhea (6.4%). In our study, pneumonia was evaluated under respiratory system diseases and acute gastroenteritis was evaluated under infectious diseases, and the most common causes of hospitalization were respiratory system diseases (54.7%) and infectious diseases (23.2%). Respiratory system diseases (40.6%) and infectious diseases (21.8%) were also the most frequent causes of hospitalization for patients with chronic diseases.

In a study conducted by De Moraes Silveira et al. (22) in 2008 on patients admitted to hospital between one month and 12 years old in Brazil, it was emphasized that patients with nutritional deficiencies had a longer hospital stay. Muñoz-Esparza et al. (23) also reported that children with critical nutritional condition at admission had a significantly longer hospital stay. In our study, while there was no significant difference between the level of malnutrition and the number of hospitalizations in patients with chronic disease, the lenght of hospitalization was found to be significantly higher in patients with malnutrition ($p=0.013$). We also found that 62.1% of the cases were hospitalized for less than 11 days, while 37.9% of them were hospitalized for more than 10 days. There were significant correlations between the lenght of hospitalization and the presence of chronic illnesses, relative weight, and BMI percentiles ($p<0.05$), while there was no significant relationship between the presence of nutritional problems, gender, age, and family income ($p>0.05$). Besides, the number of hospitalizations was found to be significantly higher in cases with chronic diseases, in the group with low relative weight and BMI percentiles, in the presence of nutritional problems and in low-income levels in our study ($p<0.05$).

We have to acknowledge some limitations of our study. Unfortunately, our study was conducted at a single center in Turkey, and the findings may not be representative of the entire country. In addition, our analysis was on infancy period. If we had evaluated a wider age range, we might have detected more important findings.

CONCLUSION

Malnutrition is still a serious public health problem, especially in developing countries like Türkiye. Mild and moderate malnutrition were detected even in patients who admitted with acute illness and were not accompanied by chronic disease. Therefore, it is important to evaluate nutritional status during hospitalization. Early diagnosis and treatment of nutritional disorders can be important in reducing mortality and morbidity. The aim of the treatment of malnutrition detected during hospitalization should be to provide better recovery and improvement, to increase the quality of life and to raise healthy individuals.

Acknowledgments

I'd like to thank all those people who helped during the development of this manuscript, by reviewing parts of the manuscript, by general feedback, or by other assistance. Those people include O.B., O.İ. and S.A.

Ethical approval

This study has been approved by the Clinical Research Ethics Committee of İzmir Tepecik Training and Research Hospital (approval date 06/05/2010, number 2010/2;6). Written informed consent was obtained from the participants.

Author contribution

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

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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NORTHWESTERN MEDICAL JOURNAL

Northwestern Med J. 2025;5(1):33-38
DOI: 10.54307/NWMJ.2025.90

RESEARCH ARTICLE

Retrospective evaluation of multiplex PCR panel results from CSF samples in a university hospital

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Cite as: Şahin F, Özcan N, Özbek E, Atmaca S, Temiz H. Retrospective evaluation of multiplex PCR panel results from CSF samples in a university hospital. Northwestern Med J. 2025;5(1):33-38.

ABSTRACT

Aim: Given the significant mortality and sequelae due to meningitis, rapid diagnosis and initiation of treatment have a major impact on patient outcomes. In many cases of meningitis/meningoencephalitis, empirical treatment should be initiated immediately. This empirical treatment regimen is initiated based on the cumulative antibiotic susceptibility results in the region. The aim of our study was to retrospectively determine the causative agents in cerebrospinal fluid samples of patients who received a presumptive diagnosis of meningitis, using Multiplex Polymerase Chain Reaction (PCR) tests.

Materials and Methods: The study included 206 cerebrospinal fluid samples from different patients with a preliminary diagnosis of meningitis sent from various clinics. The Biospeedy viral nucleic acid isolation kit (Bioeksen, Türkiye) was used for the isolation of genetic material. Genetic materials (DNA/RNA) related *to Herpes simplex virus 1-2, Humman herpesvirus 6-7-8, Varicella zoster virus, Enterovirus, Cytomegalovirus, Human Parechoviruses, Haemophilus influenzae, Listeria monocytogenes, Streptococcus pneumoniae, Neisseria meningitidis, Streptococcus agalactiae, Escherichia coli K1, Cryptococcus gattii/neoformans* in cerebrospinal fluid samples were investigated using the Meningitis/Encephalitis RT-qPCR MX-17 Panel (RT-qPCR MX-17S Panel, Bio-Speedy®, Bioeksen, Türkiye) multiplex PCR kit.

Results: According to the PCR results, the causative agent was identified in a total of 19 patients. Nine patients were found to have *Streptococcus pneumoniae*, two had *Varicella zoster virus*, and two had *Enterovirus*. Additionally, six patients had separate detections of *Haemophilus influenzae, Cytomegalovirus, Herpes simplex virus 1, Human herpesvirus 6, Human herpesvirus 8, and Parechoviruses*.

Conclusion: Recently, simple and rapid molecular tests such as PCR have contributed to an increase in the early detection of causative agents. Based on the performance of diagnostic tests, we propose an algorithm for the use of both syndromic and specific tests in patients at risk for meningitis/encephalitis.

Keywords: cerebrospinal fluid, meningitis, multiplex PCR

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Received: 01.02.2024 **Accepted:** 06.12.2024 **Published:** 31.01.2025

INTRODUCTION

Infectious meningitis and meningoencephalitis are serious, life-threatening conditions. Challenges in diagnosis continue for clinicians to initiate treatment as soon as possible. Early initiation of target-specific treatment improves the consequences of viral encephalitis or bacterial meningitis (1).

Bacterial meningitis is one of the primary infections of the central nervous system (CNS); it results from inflammation of the protective membranes covering the brain and spinal cord, known as meninges, due to bacterial infection of the cerebrospinal fluid (CSF) (2). *Haemophilus influenzae (H. influenzae), Streptococcus agalactiae (S. agalactiae),* and *Streptococcus pneumoniae (S. pneumoniae)* are among the causes of meningitis worldwide (3). The susceptibility of patients to certain pathogens appears to be age-related. In the newborns, it is usually *Escherichia coli (E. coli), Streptococcus agalactiae (S. agalactiae), Listeria monocytogenes (L. monocytogenes),* and bacteria from the *Enterobacteriaceae* family. In children, *H. influenzae* and *Neisseria meningitidis (N. Meningitidis)*; in adults, *N. meningitidis* and *S. pneumoniae* (4,5). The most common agent of viral meningitis is *Enteroviruses* (6).

Early etiologic diagnosis allows for appropriate and targeted treatment to be initiated as soon as possible. Culture of the causative microorganism is the "gold standard" for diagnosis and antimicrobial susceptibility, and culture is mandatory for community-acquired bacterial meningitis (7). In the clinical microbiology laboratory, Gram staining of CSF helps to identify the microorganism in 50-90% of cases, CSF culture is positive in approximately 80% of CSFs obtained from patients who have not started treatment (8,9). Although Gram staining is rapid and highly specific, its sensitivity is low (sensitivity varies from 10-93% depending on the use of antibiotics before taking CSF). Gram staining is most useful in the diagnosis of *S. pneumoniae* infections (1). In recent times, with the widespread adoption of molecular methods, significant contributions have been made to the identification of causative agents in meningitis (10,11). With the widespread use of molecular tests, it has been shown to be rapid, inexpensive, reliable, and effective in the identification of different agents such as bacteria, viruses, or fungi. Recent studies indicate that molecular diagnostic methods can be sensitive and specific for different microorganisms. They have been reported to be applicable in identifying pathogens in CFS from patients who have started antimicrobial treatment or have negative cultures. In addition, one of the major advantages of Polymerase Chain Reaction (PCR) is that very small amounts of clinical samples are used for molecular testing (6,11,12).

In our study, we aimed to determine infectious agents by multiplex PCR method from CSF samples sent from various clinics with a pre-diagnosis of CNS infection.

MATERIALS AND METHODS

Between January 1 and December 31, 2021, PCR results of CSF samples of 206 patients referred from different clinics of Dicle University Medical Faculty Hospital with a preliminary diagnosis of meningitis were evaluated retrospectively.

The Biospeedy viral nucleic acid isolation kit (Bioeksen, Türkiye) was used for the isolation of genetic material. After nucleic acid isolation, patient samples and PCR mixes were added to the strips in the kit on the cold tube stand in the biosafety cabinet in accordance with the manufacturer's instructions. After nucleic acid isolation, patient samples and PCR mixes were added to the strips provided in the kit, placed on a cold tube rack inside a biosafety cabinet, following the manufacturer's instructions.

Genetic materials (DNA/RNA) related *to Herpes simplex virus 1-2 (HSV 1-2), Human herpesvirus 6-7-8 (HHV 6-7-8), Varicella zoster virus (VZV), Enterovirus, Cytomegalovirus (CMV), Human Parechoviruses (HPeV), H. influenzae, L. monocytogenes, S. pneumoniae, N. meningitidis, S. agalactiae, E. coli K1, Cryptococcus gattii/ neoformans* in CSF samples were investigated using the Meningitis/Encephalitis RT-qPCR MX-17 Panel (RT-qPCR MX-17S Panel, Bio-Speedy®, Bioeksen, Türkiye) multiplex PCR kit.

The descriptive data in the study are presented with numbers and percentages for categorical data.

This study was approved by the Dicle University Medical Faculty Ethics Committee for Noninterventional

Studies (approval date 13.09.2023, number 09.2023.253). We conducted the study following the ethical principles of the Declaration of Helsinki. As this was a retrospective study, informed consent was not required.

RESULTS

CSF samples from 206 patients with a pre-diagnosis of meningitis were analyzed. According to the PCR results in our study, the causative agent was identified in 19 patients. The median age of the patients was 22 years (range: 0–67 years).

S. pneumoniae was detected in nine patients, *VZV* and *Enterovirus* in two patients each, and *H. influenzae, CMV, HHV-6, HHV-8, HSV-1,* and *HPeV* in six patients separately (Table 1). 47.4% of our patients were <18 years old and 52.6% were >18 years old (Table 2).

Table 1. The number of Meningitis Agents in the Multiplex PCR Panel

Infection Agents	Number
S. pneumoniae	9
VZV	2
Enterovirus	2
H. influenzae	1
CMV	1
HHV-6	1
HHV-8	1
HSV-1	1
HPeV	1

DISCUSSION

Infectious meningitis can be caused by many microorganisms. Despite current treatments, many types of infectious meningitis remain associated with mortality and morbidity (6). Meningitis caused by bacteria is particularly important in terms of mortality and morbidity. Despite the availability of many diagnostic methods, establishing the etiology of infectious meningitis is in many cases challenging and laborious. Physicians should consider multiple factors when assessing a meningitis patient (8). Glucose, white blood cell count, and total protein levels from CSF are all useful parameters in the diagnosis of meningitis. In spite of these 'classic' patterns, these non-specific markers are not specific enough for a definitive diagnosis. CSF culture continues to be the basis for the diagnosis of bacterial meningitis (13). In recent times, rapid tests such as the Cryptococcal Lateral Flow Assay (IMMY), FilmArray Multiplex PCR (Biofire), GeneXpert MTB/Rif Ultra (Cepheid) and Real-Time PCR have been used (6). Currently, syndrome-based tests have indicated a new approach to the diagnosis of infectious diseases, suggesting that PCR methods

Table 2. Distribution of the detected agents by age

Detected Agent	Age Range					
	0-5	5-18	18-45	45-65	>65	Total
S. pneumoniae	1	3	4	1	-	9
VZV	-	1	-	1	-	2
Enterovirus	-	2	-	-	-	2
H. influenzae	1	-	-	-	-	1
CMV	-	-	1	-	-	1
HHV-6	1	-	-	-	-	1
HHV-8	-	-	-	-	1	1
HSV-1	-	-	-	-	1	1
HPeV	-	-	1	-	-	1
Total	3	6	6	2	2	19

may be useful in the detection of meningitis. Molecular methods can determine the quantity of bacteria and detect microorganisms in the presence of antimicrobial use (11). However, with the widespread adoption of newly developed nucleic acid detection techniques, they also play an important role in the identification of viral agents. Rapid and reliable detection of viral agents prevents unnecessary antiviral use and circumvents the need for other expensive invasive tests. In a retrospective study conducted in Türkiye to investigate viral etiology, causative agents were isolated in approximately 2.3% of cases using nucleic acid tests (NAT) (14). In our study, one of the advanced diagnostic methods used was multiplex PCR.

The number of bacterial meningitis cases reported to the global surveillance center between 2006 and 2016, while the incidence in developed countries was 0.5-1.5/100,000, incidences of up to 1000 per 100,000 population have been reported, especially in west-central Africa and sub-Saharan regions (15). The symptoms of viral meningitis are generally less severe than bacterial meningitis, but identification of the causative agent is more challenging. The most common causes of viral meningitis are *Enterovirus, VZV*, and *HSV*-2 (16). In this study, the most frequently isolated agents were *S. pneumoniae*, *VZV*, and *EV*. In this study, children with *Enterovirus* were aged 5-15 years. Although enterovirus causes viral meningitis in all age groups, pediatric age is a risk factor that requires special attention (17,18). Although the bacteria that cause meningitis vary in different parts of the world, the most common causative agent worldwide is *S. pneumonia* (19).

Pean et al. retrospectively analyzed the results of 4,100 patients between April 2014 and March 2017 and reported that the most widespread causes of meningitis were *EV* 23.9%, *VZV* 10.2%, and *HSV*-2 4.2% (20). In our study, *EV* and *VZV* were detected in two different patients. Schnuriger et al. analyzed 1,744 CSF samples from 1,344 pediatric and 336 adult patients between May 2017 and November 2019 and detected, viral pathogens in 361 (21%) CSF and bacterial pathogens in 52 (3%) (21). In another study conducted over 34 months, a total of 4,199 patients' CFS were examined, and pathogens were detected in 315 (7.5%) according to Real-Time PCR results. The rate of detected pathogens was 38% for *EV*, 13% for HSV-2, and 19% for *VZV* (22). In this study, *Enterovirus* and *VZV* were the most common viral agents, while *S. pneumoniae* was the most common bacterial agent. *S. pneumoniae* is the most common etiologic agent of community-acquired bacterial meningitis (23). In Türkiye, 470 CFS were examined using Real-Time PCR to investigate the causative agents of meningitis. In the study, a bacterial or viral agent was identified in 21% (98 samples) of the sample. In total, *EV* (25%) was the most commonly detected agent, followed by *Adenovirus* (22%), and *S. pneumoniae* (15%) (24). Recent studies conducted Türkiye have reported that the causative agent of meningitis is *HSVs* (12). The *HSV* agent was detected in patients over 65 years of age, and it has been reported that the frequency of *HSV*-related infections increases at extreme ages (< 1 year and ≥ 65 years) (17). In our study, we observed that the pathogens identified were consistent with those reported in other studies (12,17,18).

Recent studies have included the comparison of the FilmArray Meningitis/Encephalitis (ME, BioFire Diagnostics) panels with other tests in identifying CNS infections. They examined a previously identified set of 291 CFS samples using the FilmArray ME panel. At the end of the study, the concordance rate was 52% (26/50) for viruses, 97.5% (78/80) for bacterial pathogens, and 90.1% (145/161) for Cryptococcus neoformans (25). In recent times, syndrome-based tests indicate a new approach to the diagnosis of infectious diseases. In a multicenter study, when the QIAstat-Dx ME Panel was compared with the BioFire FilmArray ME Panel and it was observed that they were in concordance with each other (26). Clinicians should be aware of the benefits and limitations of each test when evaluating a patient with meningitis/encephalitis, considering the potential for false-positive and false-negative results.

CONCLUSION

Timely identification of the causative agents is of critical importance in CNS infections. Traditionally, microbiological culture of CFS has been time-consuming for the identification of pathogens. Today, with the use of rapid tests such as PCR, the detection of causative pathogens can be achieved in a short period, as quick as one hour. Moreover, the microbiological culture

sensitivity of CFS decreases with the initiation of empirical treatment. Multiplex PCR panels offer many advantages over various methods in the diagnosis of CNS diseases. These panels have the capacity to rapidly detect a potentially large number of agents. This study highlights the value of rapid diagnostic methods with high levels of specificity and susceptibility to reduce the time and cost of testing, shorten the length of hospital stay and reduce antibiotic use.

Ethical approval

This study has been approved by the Dicle University Medical Faculty Ethics Committee for Noninterventional Studies (approval date 13.09.2023, number 09.2023.253). Written informed consent was obtained from the participants.

Author contribution

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

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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NORTHWESTERN MEDICAL JOURNAL

Northwestern Med J. 2025;5(1):39-45
DOI: 10.54307/NWMJ.2025.143

RESEARCH ARTICLE

The relationship between physical activity, fatigue, sleep quality, and anxiety levels of students during the university examination period

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Cite as: Baran E, Yılmaz A. The relationship between physical activity, fatigue, sleep quality, and anxiety levels of students during the university examination period. Northwestern Med J. 2025;5(1):39-45.

ABSTRACT

Aim: The aim of this study was to assess the physical activity level of university students during exam week and to investigate the relationship between physical activity level and the severity of fatigue, sleep quality, and anxiety.

Methods: Volunteers aged 18-30 years, studying in health sciences, were included in the study. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) short form, fatigue was assessed using a visual analog scale, sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), and anxiety was assessed using the State and Trait Anxiety Inventory (STAI).

Results: The mean age and body mass index of the 92 students included in the study were 21.1±2.0 years and 22.0±3.5 kg/m^2, respectively. Among the students, 38% were inactive, 56.6% were minimally active, and 5.4% were in the highly active physical activity category. There was a moderate negative correlation between IPAQ scores and fatigue (-0.449, p<0.001). Additionally, there was a moderate negative correlation between IPAQ scores and PSQI scores (-0.426, p=0.002), a moderate negative correlation between IPAQ scores and STAI-State (-0.435, p=0.001), and a weak negative correlation between IPAQ scores and STAI-Trait scores (-0.362, p=0.003).

Conclusion: Physical activity levels were found to be lower among university students during exam week compared to those reported in the literature. Additionally, as physical activity levels increased, fatigue and anxiety levels decreased and sleep quality improved. Encouraging university students to maintain adequate physical activity during exam week may be beneficial for improving fatigue, sleep quality, and anxiety.

Keywords: anxiety, exam, fatigue, physical activity, sleep quality, university students

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Received: 22.08.2024 **Accepted:** 23.12.2024 **Published:** 31.01.2025

INTRODUCTION

Physical activity is defined as the movement of the body resulting from the energy expended by the skeletal muscles in performing daily activities. Adequate physical activity is essential for maintaining a healthy life. Regular and sufficient physical activity, especially from childhood or young adulthood onwards, has positive effects on aerobic capacity, body composition, blood pressure, glucose metabolism, and physical and psychological health (1). A study analyzing the physical activity levels of 19,928 university students in 23 countries found that 23% of the students in Northwest Europe and the USA, 39% in Mediterranean countries, 30% in Central and Southern Europe, 42% in Asia-Pacific countries, and 44% in developing countries were inactive (2).

Young individuals who perform adequate physical activity have lower levels of depression and higher academic achievement (1,3). In addition, physical activity levels are directly related to quality of life, physical function, general health, physical pain, mental health, and vitality (4). Physical activity is essential for maintaining good health and reducing stress and anxiety. Exam weeks, which are a stressful time for university students, can have a significant impact on their physical and mental health. Studies have reported the positive effects of physical activity on social and personal success, sleep quality, depression levels, anxiety, and stress in healthy individuals (5-7).

Anxiety is most intense during the school exam period. Test anxiety is a specific type of anxiety experienced as a feeling of discomfort mixed with fear (1,3). Although negative conditions such as increased anxiety, stress, and fatigue levels, and deterioration in sleep quality are common during the exam period, no study has assessed the physical activity status of students during this time or examined the relationship between physical activity and fatigue severity, sleep quality, and anxiety levels. Therefore, the aim of this study was to determine the physical activity levels of university students during exam week and to investigate the relationship between physical activity levels and fatigue severity, sleep quality, and anxiety.

MATERIALS AND METHODS

The study protocol was approved by the Hitit University Ethics Committee for Non-Interventional Clinical Research (Decision No: 2023-01). Written and verbal informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Volunteers between the ages of 18 and 30 who were continuing their university education in the field of health sciences were included in the study. Individuals with orthopedic, neurological, rheumatological, oncological, mental, and cognitive diseases, and those who were currently pregnant or had a history of pregnancy or childbirth, were excluded from the study. Demographic, physical, and medical information was recorded.

Students' physical activity levels were assessed using the International Physical Activity Questionnaire - short form (IPAQ), which has been shown to be valid and reliable in Turkish. The questionnaire asks about the time spent in walking, moderate activity, vigorous activity, and sitting. The energy expenditure during physical activity is calculated by the metabolic equivalent (MET-minute) score. There are standardized MET values for different physical activities: 3.3 METs for walking, 4.0 METs for moderate physical activity, and 8.0 METs for vigorous physical activity. The calculation of these values determines the level of physical activity (inactive / minimally active / highly active) (8,9).

The fatigue felt by the students during the examination week was assessed using a 10 cm visual analog scale (VAS). On the scale, the starting point of “0 cm” means 'I do not feel tired at all,' and the endpoint of “10 cm” means 'I feel unbearably tired.' Participants were asked to mark the point on the scale that they felt was closest to their level of fatigue during the examination week. Higher scores indicate greater levels of fatigue (10).

The Pittsburgh Sleep Quality Index (PSQI) (10) assesses sleep quality and sleep disturbance. The index consists of a 19-item self-report and 7 components: subjective sleep quality, sleep duration, sleep latency,

sleep disturbance, habitual sleep efficiency, daytime dysfunction, and sleep medication use. Each sleep component is evaluated on a 0-3 point scale. The total score of the 7 dimensions gives the total scale score (between 0 and 21). A total score greater than 5 indicates poor sleep quality.

Anxiety levels were assessed using the State-Trait Anxiety Inventory (STAI), which was validated by Öner and Le Compte in 1983. This scale assesses two different parameters: the 'State Anxiety Scale' and the 'Trait Anxiety Scale.' Each scale has 20 items. The State Anxiety Scale defines how individuals feel at the assessed time and under certain conditions, and individuals should answer the items by thinking about their feelings regarding the situation they are in. The Trait Anxiety Scale assesses how the individual feels in general. The total score for both scales can range from 20 to 80, with a high score indicating a high level of anxiety and a low score indicating a low level of anxiety (11).

Statistical analysis

Statistical analyses were performed using SPSS version 22. Numerical data were analyzed using visual and analytical methods, and it was determined that the data did not meet the criteria for normal distribution. Numerical data were presented as median and interquartile range, and categorical data were presented as numbers and percentages. The relationship between physical activity levels and participants' fatigue, sleep quality, and anxiety levels was analyzed using the Spearman test. According to Spearman correlation coefficients, the degree of association was determined as follows: no association (0-0.19), weak association (0.20-0.39), moderate association (0.40-0.69), strong association (0.70-0.89), very strong association (0.90-1). In the reference study, the correlation coefficient was 0.37. Accordingly, it was calculated that 95% power could be achieved with a 95% confidence interval if at least 70 people were included in the study (12).

RESULTS

Of the 155 students who were assessed for inclusion in the study, 37 had incomplete assessments, 7 had chronic illnesses, and 4 had a history of pregnancy/maternity. Fifteen of the students did not wish to take part in the study. The assessment was completed for a total of 92 students who met the inclusion criteria. The mean age and body mass index of the 92 students included in the study were 21.1 ± 2.0 years and 22.0 ± 3.5 kg/m^2, respectively. Of those included in the study, 51 (55.4%) were female and 41 (44.6%) were male (Table 1).

Table 1. Demographic and physical characteristics of the participants (n=92)

Age (year)	21.0 (20.0-22.0)
BMI (kg/m^2)	22.09 (20.2-25.4)
Sex	
Female	51 (55.4%)
Male	41 (44.6%)
Smoking (yes %)	29 (31.5%)
Alcohol (n - %)	
Never	62 (67.4%)
Rarely	18 (19.6%)
Sometimes	12 (13.0%)
Most of the time	-
Always	-

Data are presented as median (interquartile range) or as number (percentage). BMI: Body Mass Index.

Table 2 shows the data from the participants' physical activity, fatigue, sleep quality, and anxiety

Table 2. Participants' physical activity, fatigue, body awareness, sleep quality and anxiety status (n=92)

IPAQ	960.0 (594.0-1386.0)
Inactive	35 (38%)
Minimally Active	52 (56.6%)
Highly Active	5 (5.4%)
Fatigue (cm)	6.0 (4.0-7.7)
PSQI	6.0 (4.0-7.0)
STAI-State	39.0 (33.0-49.0)
STAI-Trait	38.0 (33.0-45.7)

Data are presented as median (interquartile range) or as number (percentage). IPAQ: International Physical Activity Questionnaire-Short Form. PSQI: Pittsburgh Sleep Quality Index. STAI-State: State-Trait Anxiety Inventory. STAI-Trait: Trait Anxiety Scale.

Table 3. Relationship between physical activity values and fatigue, body awareness, sleep quality, and anxiety of the participants

	IPAQ r (p)
Fatigue (cm)	-0.449 (<0.001*)
PSQI	-0.426 (0.002*)
STAI-State	-0.435 (0.001*)
STAI-Trait	-0.362 (0.003*)

*Statistically significant association. r: Spearman correlation coefficient. IPAQ: International Physical Activity Questionnaire-Short Form. PSQI: Pittsburgh Sleep Quality Index. STAI-State: State-Trait Anxiety Inventory. STAI-Trait: Trait Anxiety Scale.

questionnaires. Among the students, 38% were inactive, 56.6% were minimally active, and 5.4% were in the highly active physical activity category.

A statistically significant relationship was observed between the physical activity levels of the participants during the exam week and their fatigue, sleep quality, and anxiety levels ($p<0.05$). There was a moderate negative correlation between IPAQ scores and fatigue (-0.449, $p<0.001$). Additionally, there was a moderate negative correlation between IPAQ scores and PSQI scores (-0.426, $p=0.002$), a moderate negative correlation between IPAQ scores and STAI-State (-0.435, $p=0.001$), and a weak negative correlation between IPAQ scores and STAI-Trait scores (-0.362, $p=0.003$) (Table 3).

DISCUSSION

The aim of this study was to determine the physical activity levels of university students during exam week and to investigate the relationship between physical activity levels and fatigue severity, sleep quality, and anxiety levels. The study found a moderate negative correlation between physical activity level and both fatigue severity and state anxiety levels, a weak negative correlation between physical activity level and trait anxiety level, and a moderate positive correlation between physical activity level and sleep quality. This study is significant because it is the first to assess the physical activity levels of university students during exam week and their relationship to fatigue, sleep quality, and anxiety.

When the physical activity levels of university students were examined during exam week, it was found that 38% were inactive, 56% were minimally active, and 5% were in the highly active physical activity category. Compared to other studies on the physical activity levels of university students, the participants in this study had lower physical activity levels (12-14). This decrease in physical activity could be attributed to stress, increased workload, and inadequate time management during exam week.

In general, sleep problems are common among university students. Poor sleep quality has been reported among students due to insufficient sleep, irregular bedtimes, use of alcohol and/or over-the-counter drugs to regulate sleep, and use of stimulants to stay awake (15,16). Smokers are known to have poorer sleep quality, as nicotine acts as a stimulant, making it difficult to fall asleep and negatively affecting sleep quality (12). In this study, the smoking habits of participants were similar to those reported in the literature, while alcohol use was found to be lower (17-19). Psychosocial and physical health problems were significantly higher among students with poor sleep quality compared to those with good sleep quality. Insomnia can lead to issues such as difficulty concentrating, irritability, fatigue, anxiety, and depression among students (20).

A moderate relationship was found between the physical activity level of university students during exam week and their sleep quality and fatigue severity. Sleep quality decreased and fatigue severity increased as physical activity levels decreased. This may be due to long study hours, stress, and inadequate time management during exam week. Physical activity has been reported to help resist fatigue by increasing muscle strength and functionality in both healthy individuals and patients of all ages. Additionally, physical activity may help students distract themselves from negative thoughts during exam week, enhancing their sense of refreshment and supporting a return to a stable physiological state. Physical activity also reduces stress, improves physiological conditions such as blood pressure, and prevents fatigue from becoming a chronic condition (5-7). Studies on physical activity and sleep disorders indicate that increasing physical activity reduces sleep disorders, while sleep problems

can decrease physical activity levels due to lethargy and daytime sleepiness. Therefore, physical activity and sleep problems have a reciprocal effect on each other (21).

The state and trait anxiety levels of the participants in this study were higher compared to the literature. Some studies report that trait anxiety is a better indicator of test anxiety than state anxiety, while others suggest that test anxiety may be related to either state anxiety or both state and trait anxiety. Exams are the most intense moments of anxiety in schools. For students, the stress of failing to meet family expectations for academic success can lead to increased anxiety (22).

Anxiety levels are expected to increase during exam week due to stress and increased workload. However, the present study found that both state and trait anxiety decreased with higher levels of physical activity. Regular physical activity is known to reduce anxiety, stress, and depression, and is associated with psychological well-being, life satisfaction, and a positive mood (23). Exercise is often the first step in lifestyle modification for the prevention and management of chronic diseases. A recent systematic review and meta-analysis found a negative association between physical activity levels and anxiety. Regular physical activity has been shown to influence the relationship between the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, regulating the release of corticotropin-releasing factor from the hypothalamus and adrenocorticotropic hormone from the anterior pituitary. These findings suggest that exercise-induced changes help modulate stress reactivity and anxiety in humans (24).

Due to stress, increased workload, and poor time management, students may experience increased sleep problems, fatigue, and anxiety during exam week. Additionally, students may limit their physical activity as they focus on studying. Physical activity is known to improve biopsychosocial well-being and is effective in managing sleep problems and fatigue. Restricting physical activity during exam week due to lack of time, stress, and workload can further exacerbate sleep problems, fatigue, and anxiety. Therefore, it is crucial to encourage students to maintain sufficient levels of physical activity during exam weeks, as recommended by physical activity guidelines, and to raise awareness about time management to allocate time for physical activity.

This study has several limitations. First, due to the transition to distance education following the earthquake on February 6, 2023, in Kahramanmaraş, an adequate number of students from each department could not be included, which prevented sub-analyses by department groups. Therefore, analyses were conducted on the overall sample. Second, students with orthopedic, neurological, oncological, or psychiatric conditions were excluded based on self-reports. Including participants after a medical examination by a physician could strengthen the findings in future studies. Lastly, the use of the IPAQ short form is a limitation. Although the short form is valid and reliable, it was chosen for its brevity due to participants' limited availability during the exam week. The long version could provide more detailed insights into different physical activity domains. Additionally, future studies may benefit from using objective tools, such as activity monitors, to improve the accuracy of physical activity data.

CONCLUSION

The results of this study showed that university students had lower levels of physical activity, higher levels of fatigue and anxiety, and poorer sleep quality during exam week compared to the literature. Additionally, there was a moderate negative relationship between physical activity levels and levels of fatigue and state anxiety, a weak negative relationship with trait anxiety, and a moderate positive relationship between physical activity levels and sleep quality. The beneficial effects of physical activity in managing fatigue, sleep disturbance, and anxiety have been well-documented in the literature. It is important to encourage university students to maintain an appropriate level of physical activity during exam week and to raise awareness of effective time management for incorporating physical activity. Moreover, universities should provide facilities such as walking areas, recreational spaces, healthy living programs, and exercise classes catering to diverse preferences to help students engage in adequate physical activity.

Ethical approval

This study has been approved by the Ethics Committee for Non-interventional Clinical Research of Hitit University (approval date 28/02/2023, number 2023-01). Written informed consent was obtained from the participants.

Author contribution

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

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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NORTHWESTERN MEDICAL JOURNAL

Northwestern Med J. 2025;5(1):46-50
DOI: 10.54307/NWMJ.2025.78

RESEARCH ARTICLE

Evaluation of hearing screening results of newborns born to SARS-CoV-2 positive pregnant women

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Cite as: Akça Ü, Sanrı E, Akça G. Evaluation of hearing screening results of newborns born to SARS-CoV-2 positive pregnant women. Northwestern Med J. 2025;5(1):46-50.

ABSTRACT

Aim: It is a scientific fact that certain viral infections during pregnancy cause hearing loss in newborns. The aim of this study was to investigate whether such infections are the cause of congenital hearing loss. This study was based on an examination of the hearing screening of newborns born to pregnant women affected by the current pandemic caused by the SARS-CoV-2 virus, which is responsible for the disease designated Coronavirus Disease 2019 (COVID-19).

Materials and Methods: In this retrospective case-control study, demographic data and ABR hearing test results of a total of 81 newborns were compared with those of 101 healthy controls. The newborns were born to mothers who tested positive for SARS-CoV-2 polymerase chain reaction (PCR) during pregnancy between March and September 2022. The mothers of the healthy controls had no problems during pregnancy.

Results: The prevalence of SARS-CoV-2 PCR positivity during pregnancy was 3.5%. A higher cesarean delivery rate was observed in the group with positive SARS-CoV-2 infection (p=0.028). The failure rate of the initial screening test was higher in both groups (22/81 vs. 25/101; p=0.712). However, a subsequent analysis revealed that there was no statistically significant difference between the results of the secondary follow-up screening (p=0.926).

Conclusion: The study data suggest that there is no indication that maternal SARS-CoV-2 infection during pregnancy results in neonatal hearing loss.

Keywords: COVID-19, hearing loss, pregnancy, newborn

INTRODUCTION

The novel strain of the virus is called SARS-CoV-2. It causes a severe illness called acute respiratory distress syndrome (1). According to the World Health Organization (WHO), more than 660 million cases of the disease have been reported worldwide as of January 2023, and more than 6.7 million deaths related to the disease have been reported. This virus, which primarily affects the respiratory system, causes damage to other organs and systems. There have also

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Received: 13.01.2024 **Accepted:** 08.11.2024 **Published:** 31.01.2025

been numerous cases of anosmia and hearing loss thought to be associated with the disease (2).

Congenital hearing loss is one of the most common birth defects. It leads to a significant delay in the child's social and language development (3). Congenital viruses such as the TORCH group viruses and Zika virus may result in fetal involvement. Direct damage to the hair cells in the inner ear and organ of Corti by these viruses may result in hearing loss in the infant (4,5). Vertical transmission of these viruses from mother to fetus has been proven. Nevertheless, the transmission route of SARS-CoV-2 remains a subject of scientific debate. The detection of angiotensin converting enzyme 2 receptor in the placenta and the presence of SARS-CoV-2 Ig M antibodies in the infant have been suggested as evidence of vertical transmission (6). Hearing screening has long been used in many countries to diagnose hearing loss at an early stage, to predict the potential outcome of treatment, and to anticipate the effects of any resulting impairment. The most commonly utilized methodologies are transient evoked otoacoustic emission (TEOAE) and automatic auditory brainstem response (AABR) tests (7). The objective of this investigation was to assess the outcomes of hearing assessments in neonates born to mothers who tested positive for SARS-CoV-2 and to determine whether these infants exhibit indications of hearing impairment.

MATERIALS AND METHODS

The present study is a retrospective analysis of newborns delivered at Samsun University Children's Hospital between March 2022 and September 2022. The necessary approval was obtained from the Scientific Research Ethics Committee of Samsun Training and Research Hospital on February 16, 2022, under the decision number 2022/3/4. The study included infants born to mothers who tested positive for SARS-CoV-2 during pregnancy and who gave birth between the specified dates. The study excluded infants with a history of asphyxia, hereditary sensorineural hearing loss in the family, TORCH infection, brain and facial anomalies, ototoxic drug use, jaundice requiring blood transfusion, and patients with a history of APGAR 1 (i.e., a minute score between 0 and 6). A control group was formed among newborns born to mothers with the same conditions and negative SARS-CoV-2 PCR test results. Gender, mode of delivery, and ABR results were categorized as non-continuous variables, whereas birth weight, maternal age, paternal age, and gestational age were categorized as continuous variables.

The statistical analysis was conducted using the SPSS 25.0 (Statistical Package for the Social Sciences, Version 25.0, Chicago, USA) statistical program. In order to facilitate the comprehension of the data, continuous variables are expressed as the mean ± standard deviation. Categorical variables are presented as percentages. The independent samples t-test was used to compare data between patients and healthy subjects. A chi-squared test (x^2) was used to facilitate comparison of data presented as percentages. Pearson's correlation coefficient was used for correlation analysis. A p-value less than 0.05 was considered statistically significant for all data.

Compliance with ethical standards

Approval was obtained from the ethics committee before the study began. The study was conducted in accordance with the principles established in the Declaration of Helsinki, and each participant provided written informed consent prior to involvement which included a detailed description of the study.

RESULTS

A total of 2,532 births occurred during the study period, and 88 pregnant women (3.5%) tested positive for SARS-CoV-2 by PCR. Eight newborns from seven pregnancies were excluded from the study because they met the established exclusion criteria. Of the eight newborns excluded from the study, four met the criteria for exposure to ototoxic drugs for more than five days, two met the criteria for multiple pregnancies resulting from twin births, and two met the criteria for being born with a birth weight of less than 1,500 grams. The study sample comprised 81 newborns, while the control group consisted of 101 newborns. No significant differences were observed between the two groups with regard to maternal age, paternal age, birth weight, gestational week, and sex (p=0.783, p=0.781, p=0.791, p=0.871, p=0.655, respectively). A

comparison of the case and control groups revealed a statistically significant difference in the rate of cesarean delivery, with a higher prevalence in the case group (p = 0.028). Demographic characteristics are presented in Table 1.

Otoscopic examination of the patients who underwent ABR testing revealed no statistically significant differences between the two groups in either the right or left ear. In the case group, 15 newborns (18.5%) exhibited bilateral referral, 5 newborns (6.2%) demonstrated right unilateral referral, and 2 newborns (2.5%) exhibited left unilateral referral. In the control group, the ABR test results were as follows: 17 newborns (16.8%) exhibited bilateral referral, 4 newborns (3.9%) exhibited a right unilateral referral, and 4 newborns (3.9%) exhibited a left unilateral referral. In the two groups, the bilateral pass result in the initial test was calculated as 59 newborns (72.8%) and 90 newborns (89.1%), respectively. A comparison of the ABR test results between the two groups did not show a statistically significant difference, as indicated by the p-value (p=0.712).

Patients who received a referral result in the initial screening underwent a repeat ABR test two weeks later. In the case group, one newborn (4.5%) exhibited a bilateral referral , while 21 newborns (95.5%) demonstrated a bilateral transition. In the control group, one newborn (4.0%) exhibited a bilateral reference result, while 24 newborns (96.0%) demonstrated a bilateral reference result. There was a statistically insignificant difference between the two groups (p=0.926). The results of the newborn hearing screening test for both groups are presented in Table 2.

DISCUSSION

Congenital hearing loss can be attributed to a number of environmental factors, including infection, the use of ototoxic drugs, premature birth, and asphyxia. Additionally, developmental and genetic causes may also contribute to this condition. Hearing loss resulting from infection can be congenital or acquired, temporary or permanent, and may manifest as sensorineural or conductive hearing loss (8). The underlying mechanisms have been identified as striae,

Table 1. A comparative analysis of the demographic and clinical characteristics of the two groups

		Maternal SARS-CoV-2 (+) group	Control group	p value*
Mother's age (min.-max.)		27.16±4.67 (19-39)	26.97±4.56 (18-41)	0.783
Father Age (min.-max.)		30.32±5.62 (19-40)	30.08±5.56 (18-39)	0.781
The infant's birth weight (in grams).		3236.66±449.74	3219.20±432.61	0.791
Birth week (min.-max.)		38.55±1.25 (37-41)	38.52±1.27 (37-41)	0.871
Gender	Female	42 (51.9%)	49 (48.5%)	0.655
	Male	39 (48.1%)	52 (51.5%)	
Mode of delivery	Vaginal delivery	24 (29.6%)	46(45.5%)	**0.028**
	Cesarean section	57 (70.4%)	55 (54.4)	

* Kruskal-Wallis H test, Pearson-χ2 cross-tab

Table 2. The results of the newborn hearing screening test for both groups

		Maternal SARS-CoV-2 (+) group (n)	Control group (n)	p value*
ABR	pass	59/81	76/101	0.712
	refer	22/81	25/101	
ABR refer	pass	21/22	24/25	0.926
	refer	1/22	1/25	

* Kruskal-Wallis H test, Pearson-χ2 cross-tab

vasculitis, direct damage to the cochlear organ or neuron, or the addition of more severe infections secondary to immune damage (7,8). In addition to TORCH group infections, Zika virus and HIV have been reported to affect the nerves on the cochlea and cause sensorineural hearing loss in newborns (4).

Three hypotheses have been proposed in studies to explain how hearing loss develops in newborns infected with SARS-CoV2 during pregnancy. The first hypothesis is that maternal infection with SARS-CoV2 would lead to infection of the fetus in utero (9). The second hypothesis is that SARS-CoV2 infection primarily causes placental dysfunction, leading to destruction of placental villi and intrauterine hypoxia (10,11). The last hypothesis is that of vertical placental transmission. It is the assumption that the physiological and immunological protection due to inflammation of the placenta is removed and the inflammation is directly transmitted to the newborn (12).

Despite the existence of studies indicating that SARS-CoV-2 virus may be associated with adverse pregnancy outcomes such as abortion, prematurity, and intrauterine growth restriction, there is currently no evidence of vertical transmission of the virus (13-15). These complications are believed to be due to the systemic effects of the virus on the mother. It has been argued that a significant cytokine storm, especially in severe infections, causes neuronal defects in the fetus due to the proinflammatory period in the first and third trimesters. While vertical transmission has not been proven, the toxic effect of increased TNF-alpha levels in the placenta on the fetus has been emphasized in studies (16,17).

The results of the limited number of studies conducted on this topic are mixed. In a study conducted in 2022, the amplitudes of transient evoked otoacoustic emissions (TEOAE) were found to be reduced in asymptomatic patients with confirmed SARS-CoV-2 infection compared to a control group. Additionally, the study demonstrated the deleterious effects of SARS-CoV-2 on hair cells in the cochlea (18). Kilic et al. (17) reported five patients who developed sudden unilateral sensorineural hearing loss. Conversely, Veeranna et al. (19) observed comparable TEOAE results between the two groups and noted a significant prolongation of the intertopic intervals, suggesting that while impairment of cochlear function is unlikely, ABR function may be potentially affected. Celik et al. demonstrated that infants born to mothers with intrauterine SARS-CoV-2 infection may have a disorder of the medial olivary efferent system (20). In a recent study, Alan et al. proposed that disease during pregnancy may increase the risk of hearing loss in newborns (21). Their findings indicated a higher prevalence of SARS-CoV-2 positivity in the first ABR compared to the control group. In contrast, the four most recent studies indicated no association between SARS-CoV-2 infection and hearing loss in newborns (21-25). Our findings did not show statistical significance in the prevalence of hearing loss between the two groups in the cohort.

CONCLUSION

The results of the current hearing screening indicate that there is no evidence of congenital hearing loss in newborns born to SARS-CoV-2 PCR-positive pregnant women. However, since hearing loss may develop later in life, it is recommended to plan studies with long-term follow-up and more comprehensive technical analyses.

Ethical approval

This study has been approved by the Ethics Committee of Samsun Training and Research Hospital (approval date 16/02/2022, number 2022/3/4). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: ÜA Concept: GA; Data Collection or Processing: ES; Analysis or Interpretation: ÜA; Literature Search: GA, EA; Writing: ÜA. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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NORTHWESTERN MEDICAL JOURNAL

Northwestern Med J. 2025;5(1):51-55
DOI: 10.54307/NWMJ.2025.117

CASE REPORT

Minimally invasive treatment of the cyst of the canal of Nuck with the laparoscopic total extraperitoneal approach

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* This paper has been presented as a poster in 6th International Koru Pregnancy, Delivery and Puerperium Congress organized between April 27th, 2023, and April 30th, 2023, in Bolu, Türkiye.

Cite as: Mete Ural Ü, Şengül N, Esmer EB, Aydın E, Erdoğan Düzcü S. Minimally invasive treatment of the cyst of the canal of Nuck with the laparoscopic total extraperitoneal approach. Northwestern Med J. 2025;5(1):51-55.

ABSTRACT

The cyst of the canal of Nuck (CCN) is an extremely rare pathology that occurs as a result of the inability to obliterate the processus vaginalis. No standard therapeutic procedure currently exists, and the condition remains unfamiliar to gynecologists. In this report, we aimed to discuss the treatment of CCN with a minimally invasive method. A 33-year-old woman diagnosed with the CCN was treated with a laparoscopic total extraperitoneal approach with the best postoperative recovery. Awareness of CNN is critical for appropriate diagnosis and management. The classic treatment is excision of the cyst and closure of the inguinal ring as an inguinal hernia operation. The laparoscopic total extraperitoneal approach is a minimally invasive and effective treatment method that can be applied as an alternative to classical surgical treatment.

Keywords: canal of Nuck, cyst, endometriosis, laparoscopy, total extraperitoneal approach

INTRODUCTION

The canal of Nuck (CN) is a female analog of the patent processus vaginalis in the male. The cyst of the canal of Nuck (CCN) is formed by the peritoneal pocket extending into the inguinal canal along with the round ligament, resulting from the failure of the closure of the processus vaginalis (1). Anton Nuck provided the earliest description of it in 1650 (2). In the literature a variety of definitions are used for this extremely rare condition, including female hydrocele, Nuck canal hydrocele, Nuck's diverticulum, and cyst of the canal of Nuck. The origin of this very rare disease, especially in adulthood, is rooted in embryogenesis (3).

CCN often presents clinically as a genital or groin swelling, which permits a wide range of potential diagnosis. Due to its rarity, the CCN is frequently

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Received: 20.05.2024 **Accepted:** 15.08.2024 **Published:** 31.01.2025

misdiagnosed because most medical experts are unaware of its existence. A thorough clinical examination and sufficient radiologic imaging are required to determine a precise diagnosis. The treatment is surgical excision. The laparoscopic total extraperitoneal (TEP) approach, without an incision of the peritoneal cavity, reduces surgical trauma and hastens the healing of postoperative wounds. In this case, the successful treatment of a large CNN with the laparoscopic TEP technique is presented.

CASE REPORT

A 33-year-old female patient presented to the gynecology outpatient clinic with swelling of the left inguinal region that had persisted for the last three months. She had a surgical history of cesarean section and previous right kidney transplantation. In the physical examination, a smooth-surfaced, mobile mass of 6-7 cm in diameter expanding from the left inguinal area to the labium majus was observed (Figure 1.a). There was no difference in mass dimensions with the Valsalva maneuver. To observe the intra-abdominal relationship of the mass, computed tomography was performed and a 70×53×44 mm simple-looking, thin-walled cyst was observed outside the left inguinal canal, unrelated to the abdomen, and was evaluated as a CCN (Figure 1.b). The patient was consulted to the department of gastroenterological surgery, and it was decided to remove the cyst with the TEP technique as she had previously undergone kidney transplantation and cesarean section. The cyst capsule was completely excised by TEP approach (Figure 2.a,b). Obliteration of the inguinal canal was achieved by placing a mesh on the anterior abdominal wall and the procedure was terminated.

The histopathology report confirmed endometriosis in the cyst wall. While the cyst epithelium showed positive staining with calretinin, CD10 positive staining was seen in the stroma in the endometriosis focus, and estrogen receptor positive staining was seen in the endometrial glands (Figure 3.a,b). The patient was discharged uneventfully on the second postoperative day and her control evaluation one week later was normal. The patient signed the informed consent form and consented to the publication of her photographs.

DISCUSSION

The portion of the processus vaginalis that is found in the inguinal canal of females is known as the canal of Nuck (CN) (2). The processus vaginalis normally closes during the first year of life. Disorders of the canal most often affect young girls under the age of five (3). Even fewer cases occur in adults. Failure to completely obliterate the CN results in several diseases, including herniation of intraabdominal organs involving intestinal and genital contents, such as the uterus, fallopian tube, and ovary and hydrocele of the CN (4). The hydrocele of the CN is also called CCN.

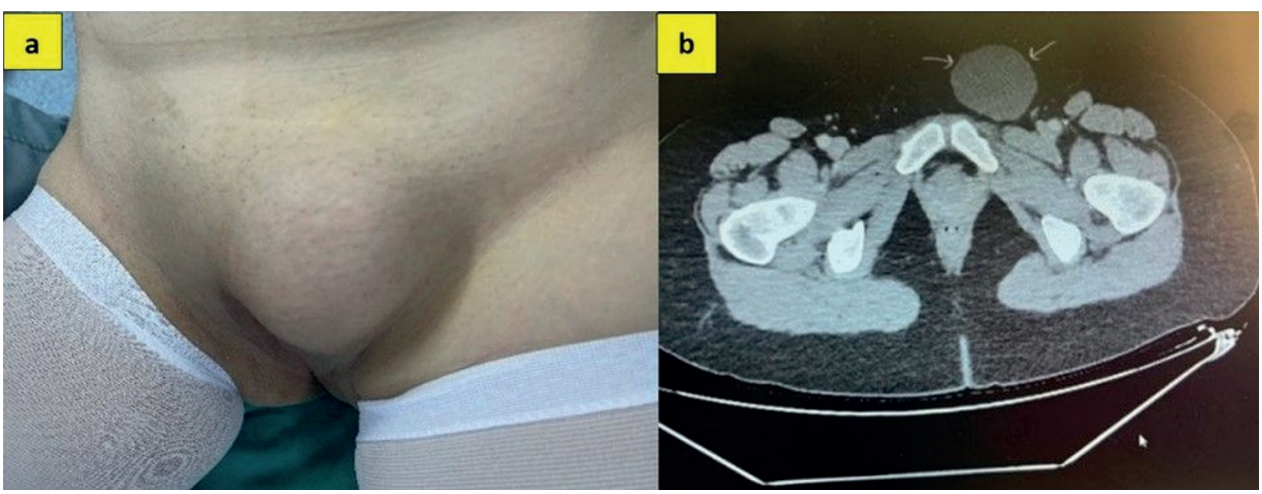

Figure 1. a: Swelling in the left groin region, **b:** Thin-walled anechoic cyst outside the inguinal canal.

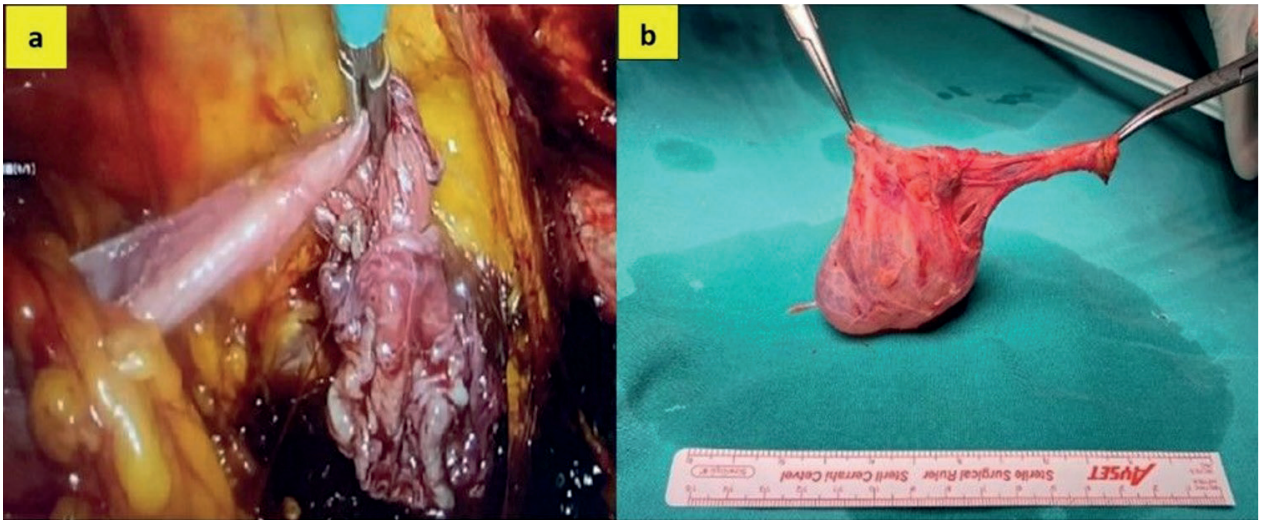

Figure 2. a: Cyst capsule stripped of round ligament, **b:** Totally excised cyst capsule.

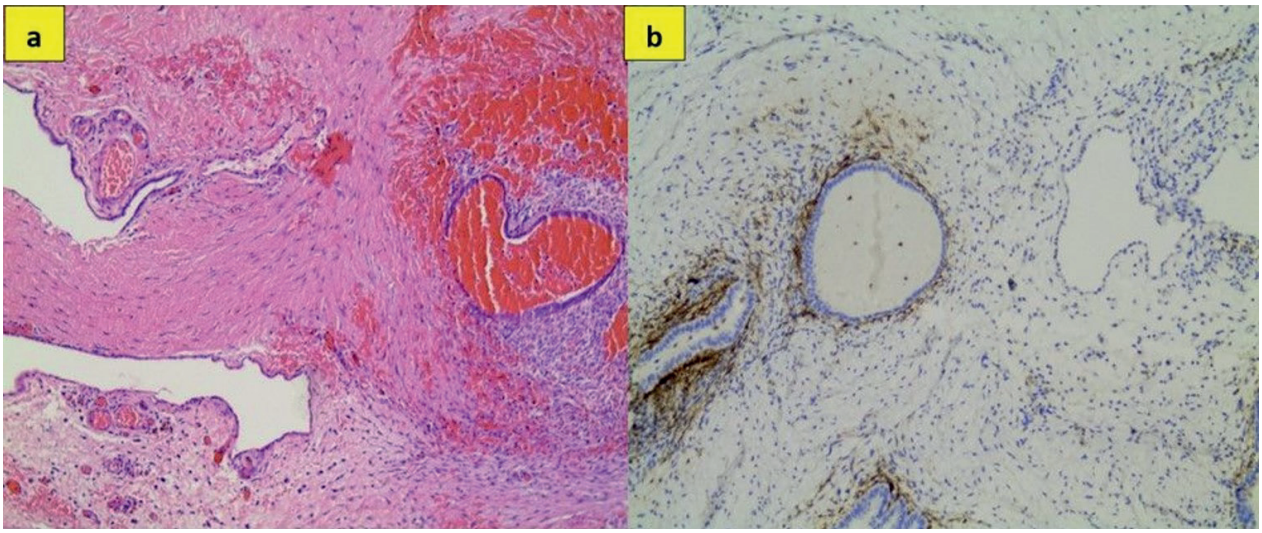

Figure 3. a: Endometriosis focus in Nuck's canal cyst wall covered with cuboidal epithelium, HEX100 (hematoxylin and eosin staining), **b:** CD10 (B Cell Development Marker) positive staining of the stroma in the focus of endometriosis, CD10X100.

Clinically, CCN may present as an inguinal mass that is either painless or painful, fluctuant, movable, and irreducible, without associated nausea or vomiting. As a result, identifying this entity solely based on clinical findings is challenging. This mass typically expands to the labia majora during the Valsalva maneuver and does not expand. Inguinal hernia is the most significant differential diagnosis for CCN. Additionally, diagnoses of lymphadenitis, lipoma, leiomyoma, sarcoma, cyst, and abscess should be taken into account (4). Endometriosis has also been reported in cases of CN, which is relatively uncommon and makes diagnosis difficult in many instances. The possibility of endometrial tissue seeding in CN is extremely rare. To the best of our knowledge, very few cases of endometriosis of the CN have been documented in the literature (5-7). Cancer development that originated from endometriosis in the CN has also been reported

(6). In our case, endometriotic lesions that had developed in the CN were detected.

Due to the extreme rarity of CCN, there is still no established standard of a therapeutic procedure, and professionals are unfamiliar with the disorder. Excision of the hydrocele and closure of the enlarged inguinal ring are the suggested treatment options. A conventional open anterior technique is typically used to accomplish this through the inguinal canal. Over the past decade, the laparoscopic approach to inguinal hernia treatment has advanced quickly. The laparoscopic TEP procedure is an effective, minimally invasive method for treating hernias that doesn't require entering the peritoneal cavity (8).

The TEP technique is considered a popular laparoscopic method that can also be used in the treatment of CCN (9). The use of TEP approach in the surgical treatment of CCN is very rare in the literature (10). Gynecologists have limited experience with the anatomy of the inguinal canal and the laparoscopic total extraperitoneal approach to this region. Collaborating with general surgeons who use the TEP technique extensively and following technological developments can provide advances in patient management. A concomitant inguinal hernia can occur in about one-third of patients with a CCN, necessitating simultaneous repair (5). It is possible to treat the inguinal hernia concurrently during the CCN excision.

Since there is no intervention to the peritoneum in the laparoscopic TEP approach, patients recover faster and experience fewer recurrences than those who undergo standard anterior surgery (9). After the cyst is removed surgically, it's crucial to cover the canal with mesh to prevent recurrence and hernia development (10). With the TEP technique, mesh placement can also be achieved practically (8).

Laparoscopic TEP repair shortens the length of the procedure, reduces bleeding volume, improves intraoperative indices, diminishes postoperative discomfort, lowers the risk of infections and sequelae, causes less damage to normal tissues, promotes better postoperative recovery, and leads to a shorter hospital stay. This technique provides convenience in cases of recurrent inguinal hernia and in obese patients. It has excellent potential for clinical advancement (9).

Disadvantages of the TEP technique include technical challenges due to the unfamiliar pelvic anatomy and the small working area, prior surgeries, and a long learning curve. Because of the restricted view of the inguinal anatomy, the distal end of the cyst removal is difficult and necessitates specialized knowledge, practice, and experience for the laparoscopic TEP approach (10). Although the cyst was completely outside of the inguinal canal towards the labia majora, because of the history of two previous surgeries in our case, it was completely removed by applying the successful TEP procedure.

CCN should be kept in mind in the differential diagnosis of women with a mass in the inguinal region, and the TEP technique is an effective and minimally invasive method that should be considered as an alternative in the surgical treatment of these patients.

Ethical approval

Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: UMU, NŞ; Concept: UMU, NŞ; Design: UMU, NŞ; Data Collection or Processing: EBE, EA; Literature Search: UMU, SED; Writing: UMU, EBE. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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NORTHWESTERN MEDICAL JOURNAL

Northwestern Med J. 2025;5(1):56-59
DOI: 10.54307/NWMJ.2025.178

CASE REPORT

A rare case report: desmoid-type fibromatosis

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Cite as: Küçüköztaş N, Başaran E, Eksert YE, Dereli M. A rare case report: desmoid-type fibromatosis. Northwestern Med J. 2025;5(1):56-59.

ABSTRACT

Desmoid tumors, also known as desmoid-type fibromatosis (DF), develop from musculoaponeurotic tissues. They are fibrous tumors of benign character that do not metastasize. However, they can take an aggressive course by showing local growth in the area where they are located. Although they can originate fromany skeletal muscle, they are most commonly seen on the anterior abdominal wall. Various treatment options are available depending on the clinical condition of the patient. We aimed to discuss the diagnosis and treatment of DF with a 55-year-old male patient who has DF and applied to our clinic.

Keywords: mesenchymal tumor, fibrous type, local growth

INTRODUCTION

Desmoid-type fibromatosis (DF) is a rare, locally infiltrative, mesenchymal neoplasm associated with local recurrence but without the potential for metastasis. DF accounts for 0.03% of all neoplasms and 3% of soft tissue tumors. It occurs most commonly between the ages of 10 and 40 and is the most common cause of anterior abdominal wall mass in young women of childbearing age (1). DF tends to develop in surgical scarring sites, especially after cesarean sections and intra-abdominal resections (2). Trauma, pregnancy, and the use of oral contraceptives play a role in etiopathogenesis (3). However, it can affect almost any part of the body, including the extremities, head and neck, trunk, and abdominal cavity. Although the vast majority of these tumors are sporadic, DF can also be hereditary (1). Familial DF develops predominantly in patients with familial adenomatosis polyposis (FAP). The risk of developing DF in patients with FAP is 1,000 times greater (2). However, in about 90 percent of cases, no cause can be found. In sporadic cases, it is characterized by a mutation in the CTNNB1 (cadherin-associated protein beta 1) gene. In hereditary cases, 5–15% are associated with the APC adenomatous polyposis coli gene mutation. There may be an abnormal accumulation of β-catenin within the cell in both hereditary and sporadic cases (4). Granular nuclear expression of catechins is found in approximately 80% of neoplasms (1).

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Received: 29.09.2023 **Accepted:** 11.12.2023 **Published:** 31.01.2025

The diagnosis is made by histopathological evaluation. Depending on the location of the tumor, ultrasound, computed tomography, and magnetic resonance are the main imaging methods (4).

Histopathologically, DF is usually infiltrative and consists of sweeping fascicles of uniform myofibroblasts within a dense collagenous stroma. The histological differential diagnosis ranges from scar formation to abdominal gastrointestinal stromal tumors and "low-grade liposarcoma" to a wide range of spindle cell lesions (1).

Clinical presentation ranges from asymptomatic to pain, paresthesia, and intestinal obstruction. DF treatment includes combinations of surgery, radiation therapy, and systemic therapy (5).

CASE

A 55 year old male patient, with no known extracomorbidity, underwent surgery for a mass in his small intestine as a result of the examinations conducted in an external center. He had complaints of abdominal pain, nausea, green-colored vomiting, and weight loss of 20 kg in the last two months. No remarkable pathological finding revealed in laboratory tests. When we questioned the family history of the patient, it was learned that his father had died of lung cancer. The patient's upper gastrointestinal endoscopy and colonoscopy were negative for malignancies. A large number of polyps, measuring 11x7 mm in size, were observed in the gallbladder lumen in the entire abdominal USG of the patient. Free fluid was detected in the pelvis in the form of smearing.

A contrast-enhanced CT of the upper abdomen showed a mass in the distal jejunum, which was primarily evaluated for carcinoma, and a pleural effusion in the right abdomen. During the surgery for excision of the mass, a white solid lesion (3.5x2.5x3.5 cm) was observed. There was no direct relationship between the lesion and the intestinal lumen. In the pathological examination of the lesion material, beta-catenin (+), desmin (-), SMA (weak +), CD117 (-), CD34 (-), DOG-1 (-), and Ki67 (proliferation index up to 3%) were found. Because the patient's symptoms persisted, Pet CT was performed. 3 lesions (SUVmax = 5.0), the largest of which was 5.5 cm in diameter were detected. Additionally, increased FDG uptake in the serosal peritoneal surfaces of the were seen in PET CT. The effusion accompanied by minimal FDG uptakes in the pelvis was thought to be benign.

Diffuse and linear atelectatic changes in both lungs were reported as pleural thickening, mostly in the field, on a thorax CT performed as the patient's complaints continued. The patient was operated because of a large lesion caused ileus in the left lower quadrant, which seen on CT. As a result of the examination of the pathological sample taken during the operation, a white solid lesion (3.5x2.5x3.5 cm) was observed when the serosa was sectioned. In the subsequent comparative abdominal CT, no mass causing ileus was observed in the left lower quadrant, but stable solid masses, the larger ones in the left upper quadrant, were observed in the mesentery. Tamoxifen (2x20 mg) was prescribed to the patient whose pathological diagnosis was desmoid-type fibromatosis.

DISCUSSION

DF accounts for 0.03% of all neoplasms and 3% of soft tissue tumors (6). The aannual incidence is reported to be 2-4 people per million. It was the first DF case that we have seen in our 13 years of clinical experience in oncology. Although most DF are sporadic, incidences related to familial adenomatous polyposis (FAP) were reported to range between 7.5% and 16% (7). About 85 to 95% of sporadic DFs are characterized by activating mutations in the exon 3 of the CTNNB1 gene (8). According to various studies, DF most commonly occurs between the third and fourth decades of life, where both sexes are almost equally affected (6,8). Some studies indicate that 9-16 year olds are affected (9). Our patient was much older than cases who are reported in the literature. Abdominal type is the most common type, with up to 37% to 50% reported in various publications (10). Our case was an abdominal DF.

One of the effective treatment method for abdominal desmoid tumors is resection and abdominal reconstruction. Some studies show that the average period of local nuclei development for patients with desmoid fibromatosis diagnosis in abdominal wall with

negative surgical borders is 83.4 months and 13.1 months for patients with positive surgical borders. Radiotherapy can provide 75-80% local control in large populations or in cases where the surgical borders cannot be macroscopically clear (11). Studies are available for systemic treatment options in patients where negative surgical borders are not met. Our patient also needed additional systemic treatment due to the residual tumor. Pharmacological treatment of desmoid tumors includes non-steroidal anti-inflammatory drugs (NSAIDs), such as methotrexate, and low-dose chemotherapeutic drugs such as vinblastine and vinorelbine. In addition, any of the tyrosine kinase inhibitors (TKI) can be used, including imatinib, sunitinib, and sorafenib (12).

In the study made by van Maren et al. both pazopanib and sorafenib were found effective. Liposomal doxorubicin is also recommended for the treatment of abdominal desmoid tumors (9). Systemic treatment options include antihormonal treatment, regardless of the presence of ER/PR positivity. Antihormonal agents such as Tamoxifen can be used as first-line treatment alone or in combination with NSAIDs, with limited toxicity, rare side effects, and low costs (13,14). That's why we chose the tamoxifen treatment in our case and we are still monitoring the patient in remission with tamoxifen. Bini et al. (15) reported that the disease is very rare and may occur spontaaneously. van Maren et al. (9) used a combination of vinorelbine, methotrexate, and thalidomide, doxorubicin. Response rates of 19.2-40% have been reported (9). We think we result is important for our patient to guide further treatment steps.

CONCLUSION

As a result, it is difficult to establish a standard treatment regimen for DF. Some studies suggest that various treatment options, such as surgery, radiotherapy, and systemic treatment can be used. Although the disease does not cause metastases, it can affect the quality of life of the individual. In these patients, a treatment decision must be made with a multidisciplinary approach and consideration of the literature.

Ethical approval

Written informed consent was obtained from the participants.

Author contribution

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

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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ISSN: 2979-9538