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ORIGINAL ARTICLE

The clinical frailty scale for the assessment of frailty in octogenarians in the intensive care unit

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ABSTRACT

Objective: Increased frailty is shown to be related to vulnerability to adverse health outcomes. The objective of the study was to assess the usability of frailty identified using the Clinical Frailty Scale (CFS) in patients aged 80 years and older admitted to the intensive care unit (ICU).

Materials and Methods: We conducted a retrospective screening of the octogenarian patients admitted to the ICU between January 1 and October 31, 2023. After excluding the postoperative patients, we recorded the demographic characteristics and comorbidities, APACHE II scores, Charlson Comorbidity Index, CFS scores, general admission reasons, and discharge patterns from ICU.

Results: The median age of the 156 patients in the study was 85, with 51.9% being female. The median APACHE II score was 18 (12–28), and the median CFS score was 5 (1–9). The CFS score categorized 37 patients as non-frail, 37 as pre-frail, and 82 as frail. The frail group exhibited statistically significant elevations in age, albumin levels, APACHE II scores, and comorbidities, including dementia, cerebrovascular disease, and cancer. The CFS score, age of 90 years or older, presence of pressure ulcers, APACHE II score, and acute kidney injury were associated with an increased risk of mortality. However, analysis of survival rates across frailty categories revealed no significant differences among the groups (p: 0.348).

Conclusion: Although the survival analysis revealed no major differences among non-frail, pre-frail, and frail groups, frailty was associated with risk of death in patients aged 80 and older, making it a potentially simple tool for doctors to predict outcomes.

Keywords: frality, octogenarian, intensive care, mortality, geriatrics

INTRODUCTION

Advances in health technology and healthcare have led to longer lifespans, resulting in an increasing proportion of elderly patients in the population. Global life expectancy rose from 34 years in 1913 to 72 years in 2022 and is projected to surpass 77 years by 2050 [1]. Furthermore, according to the Organization for Economic Cooperation and Development (OECD), the average life expectancy of people 65 years old was 19.9 years [2]. The International Monetary Fund (IMF) reports that people over 80 will make up 5% of the population by 2050 [3]. As the population ages, there will be a rise in geriatric health issues to address. In addition, an increase in the number of elderly individuals leads to a corresponding rise in geriatric hospital admissions and admissions to the intensive care unit (ICU).

Frailty is most commonly used to define the deterioration in physical, psychological, and cognitive functions caused by aging [4]. Frail

individuals have been shown to be more susceptible to acute illnesses, more prone to experience complications related to medical interventions, and more likely to face adverse outcomes associated with both surgical and non-surgical issues as well as mortality [4-7]. Whether referred to as a "syndrome" or "state," it is a determinant of both mortality and morbidity, with many scales developed to assess the degree of frailty [8]. The Clinical Frailty Scale (CFS), defined by Rockwood et al. is one of the most widely used tools and is scored on a 9-point scale [9]. It is a comprehensive scale that includes judgments on comorbidities, cognitive status, and disability, making it useful for assessing pre-hospital frailty status [10], predicting surgical outcomes [11], and monitoring critically ill patients [12-14].

It was reported that in patients aged ≥65 years, the CFS is strongly associated with both short- and long-term mortality, length of hospital stay, all-cause readmission, and unfavorable discharge destination [14,15]. A study involving patients from ICUs across European countries found that CFS correlated with in-ICU and short-term mortality in octogenarians [16]. The current study aims to investigate the all-cause in-ICU mortality of octogenarian patients in an ICU in a non-European country with a distinct healthcare system.

MATERIAL AND METHODS

This retrospectively designed study was carried out at the ICU at the Ministry of Health, Etlik City Hospital. The study included patients aged 80 and older who had been admitted to the ICU from January 1, 2023, until October 1, 2023. We excluded those who died within the first 24 hours of ICU admission. Due to the short ICU stays of most postoperative patients, we also excluded them to mitigate potential bias in the data. We used the hospital's data recording system to obtain details on demographics, dates of admission, discharge, or death, and laboratory findings. In addition to the CFS, the APACHE II and Charlson Comorbidity Index scores were computed.

The clinical frailty scale (CFS)

The CFS was originally developed to determine the overall fitness or frailty of older patients [9]. The 9-point tool, based on clinical judgment rather than questions, enables the assessment of the baseline clinical status of the individual at the onset of a new condition (ICU admission in this study) to predict prognosis, risk of death, or the outcomes of the previously defined condition [17-19]. The higher score means the more frailty. While a score of 1 denotes a very fit individual who is robust, active, and energetic and able to exercise regularly, a score of 9 defines a terminally ill person experiencing severe frailty and a life expectancy of less than 6 months [17]. The CFS categorizes scores of 1 to 3 as non-frail, a score of 4 as pre-frail, and scores ranging from 5 to 9 as frail [20]. The patient's acute clinical condition may influence the CFS assessment; therefore, baseline frailty status was obtained from their caregivers. Frailty assessments were conducted by a 3-year experienced geriatrician using the Turkish validated version of CFS [19].

Ethics approval

The study protocol adhered to the principles of the Declaration of Helsinki. The hospital's local ethics committee approved the study protocol (AESH-EK1-2023-764).

Statistical analysis

Descriptive statistics were made for the demographics, clinical scores, and laboratory. Pearson's chi-square test was used. The Kruskal-Wallis test analyzed the frailty categories, and a pairwise comparison test compared distinct variables. Post-hoc pairwise comparisons between the three groups were conducted using the Bonferroni correction to adjust for multiple testing.

Cox regression analysis was done to investigate the relationship between independent variables and mortality. For 30-day survival, we performed a Kaplan-Meier survival analysis. The sample size was determined to be 126 based on the existing literature on CFS in the intensive care unit, using the Spearman Correlation Test, assuming an expected moderate correlation (0.3) and a significance threshold (α) of 0.05, to achieve a statistical power (β) of 0.80. We used a p-value of less than 0.05 to indicate statistical significance. IBM SPSS software version 26.0 was utilized for statistical analysis.

RESULTS

After reviewing 208 subjects ≥80 years old, excluding those who passed away within the first 24 hours of ICU admission and those admitted for postoperative care, the study comprised 156 patients. The median age was 85 years (min-max: 80-101), and 81 (51.9%) of the participants were female. 106 patients (67.9%) were transported from the emergency room (ER), while 50 patients (31.1%) were transferred from the ward. The median length of stay (LOS) in ICU was 6 days (min-max: 1-49). The median APACHE II score was 18 (min-max: 12-28), the median Charlson comorbidity index score was 7 (min-max: 15), and the median CFS was 5 (min-max: 1-9). Upon ICU admission, the laboratory reported a mean hemoglobin value of 10.7 g/dL (SD: ±2.57) and a median albumin value of 29.3 g/L (min- max 16.9-44.3) (Table 1).

The most common causes for ICU admission were infections and respiratory failure (84.6% and 54.5%, respectively). Of the patients with an infection, 99 (75%) had pneumonia, 44 (33.3%) had urinary tract infections (UTI), 7 (5.3%) had cholecystitis, and 5 (3.2%) had central catheter infections. The gastrointestinal system (11, 73.3%) was the major site for bleeding. 111 (71.6%) individuals had acute kidney injury (AKI) either on admission or during the ICU stay. 44 (28.2%) of them suffered from pressure injuries. During the ICU stay, 76 (48.7%) of the patients required invasive mechanical ventilation, of whom 9 (11.8%) were extubated, and 9 (11.8%) had percutaneous dilatational tracheostomy. The in-ICU mortality rate was 37.2%. Among patients discharged from ICU, 72 (46.1%) were transported to the ward and 26 (16.7%) to the palliative care service. Considering the relationship between mortality and follow-up parameters, being ≥ 90 years old (p:0.029), the APACHE II score (p:0.004), the CFS score (p:0.004), having a pressure injury (p:0.003), and having AKI were found to be significantly correlated with mortality (Table 2).

The study population was compared based on the CFS classification as non-frail, pre-frail, or frail. The frail group was significantly older (p:0.039). Cerebrovascular disease, dementia, and cancer were more common in the frail group (p:0.001, p<0.001, p:0.037, respectively). Cardiovascular disorders and AKI as an acute illness were more common in the frail group (p:0.035, p:0.044, respectively) (Table 2).

Table 1. Demographics and basal measurements

Parameters, (n=156)	
Age	85 (80-101)
Gender, female n (%)	81 (51.9%)
APACHE II score (med, min-max)	18 (12-28)
Charlson Comorbidity Index (med, min-max)	7 (1-15)
CFS (med, min-max)	5 (1-9)
Albumin at hospitalization (g/L) (med, min-max)	29.3 (16.9-44.3)
Hemoglobin at hospitalization (g/dL) (mean±SD)	10.77±2.57
Site of transfer to the ICU	
Emergency room:	106 patients (67.9%)
Ward:	50 patients (32.1%)
Comorbidities	
Hypertension	86 (55.1%)
Diabetes mellitus	57 (36.5%)
Coronary artery diseases	44 (28.2%)
Heart failure	49 (31.4%)
Chronic lung diseases	31 (19.9%)
Chronic kidney diseases	23 (14.7%)
Dementia	37 (23.7%)
Cerebrovascular diseases	20 (12.8%)
Cancer	35 (22.4%)
Acute problems during ICU stay	
Respiratory failure	85 (54.5%)
Cardiovasculary problems	32 (20.5%)
Oral intake disorders	45 (28.8%)
Cerebrovascular problems	12 (7.7%)
Bleeding	15 (9.6%)
Acute kidney injury	111(71.6%)
Infections	132(84.6%)
Pneumonia	99(63.5%)
Urinary tract infections	44(28.4%)
Biliary tract infections	9(6.8%)
Meningitis	3 (2.2%)
Others	8(6.0%)
Endotracheal intubation	76 patients (48.7%)
Duration of ICU stay	6 days (min:1-max:49)
Exitus	58 (37.2%)
To palliative service	26 (16.7%)
To ward	72 (46.1%)

CFS: Clinical Frailty Scale, med: median, min: minimum, max: maximum, SD: standard deviation, g: gram, dL: desiliter, L: liter, ICU: intensive care unit

Table 2. Comparison of the patients according to frailty categories

	NON-FRAIL (37)	PRE-FRAIL (37)	FRAIL (82)	p
Age (median, min-max)	83 (80-94)	85 (80-97)	85,5 (80-101)[a]	0.039
Age category, n(%)				
80-89	33 (89.2)	29 (78.4)	57 (69.5)	0.062
≥ 90	4 (10.8)	8 (21.6)	25 (30.5)	
Gender, female, n (%)	16 (43.2)	22 (59.5)	43 (52.4)	0.374
APACHE II score	14 (12-18)	18 (12-28) [a]	18.5 (12-28) [a]	0.001
Haemoglobin (median, min-max)	11.5 (6.6-18.1)	10.8 (5.6-14.3)	10.4 (4.7-15.7)	0.193
Plasma albumin, (median, min-max)	31.9 (16.9-44.3)	30.2 (21-41.4)	26.8 (17.4-43.0) [a]	0.002
Charlson comorbidity index, (median, min-max)	6 (4-11)	6 (5-15)	8 (5-15) [a,b]	<0.001
Endotracheal intubation, n (%)	14 (37.8%)	18 (48.6%)	44 (53.7)	0.279
Mortality, n (%)	11 (29.7)	11(29.7)	36 (43.9)	0.188
Comorbidities				
Hypertension, n (%)	15 (40.5)	20 (54.1)	51 (62.2)	0.088
Diabetes mellitus, n (%)	14 (37.8)	14 (37.8)	29 (35.4)	0.950
Coronary artery disease, n (%)	12 (32.4)	9 (24.3)	23 (28.0)	0.740
Heart failure, n (%)	11 (29.7)	14 (37.8)	24 (29.3)	0.627
Chronic lung disorder, n (%)	8 (21.6)	8 (21.6)	15 (18.3)	0.873
Chronic kidney disease, n (%)	3 (8.1)	4 (10.8)	16 (19.5)	0.198
Dementia, n (%)	1 (2.7)	6 (16,2)	30 (36.6)[a]	<0.001
Cerebrovascular disease, n (%)	1 (2.7)	1 (2.7)	18 (21.9)[a,b]	0.001
Cancer, n (%)	8 (21.6)	3 (8.1)	24 (29.7)[b]	0.037
Acute problems during ICU stay				
Acute respiratory failure, n (%)	21 (56.8)	21 (56.8)	43 (52.4)	0.864
Cardiovascular, n (%)	3 (8.1)	12 (32.4)[a]	17 (20.7)	0.035
Impared oral intake , n (%)	6 (16.2)	10 (27.0)	29 (35.4)	0.099
Neurological , n (%)	3 (8.1)	3 (8.1)	6 (7.3)	1.000
Bleeding, n (%)	4 (10.8)	3 (8.1)	8 (9.8)	1.000
Infections, n (%)	31 (83.8)	28 (75.7)	73 (89.0)	0.172
Acute kidney injury, n (%)	27 (73.0)	37 (100)	52 (63.4)[b]	0.044

n: number, min: minimum, max: maximum

ab: intragroup Bonferoni post hoc test value

a: signifcant diferences to non- frail

b: signifcant diferences to pre-frail

The survival rate did not differ significantly between groups (p:0,348) (Figure 1).

Cox regression analysis revealed that age, presence of a pressure injury, presence of AKI, APACHE II score, and CFS were independently associated with mortality (Table 3). The overall model was statistically significant according to the Omnibus Test of Model Coefficients (χ^2 = 41.997, df = 6, p <0.001), and the –2 Log Likelihood value for the final model was 436.156, demonstrating an adequate fit to the data.

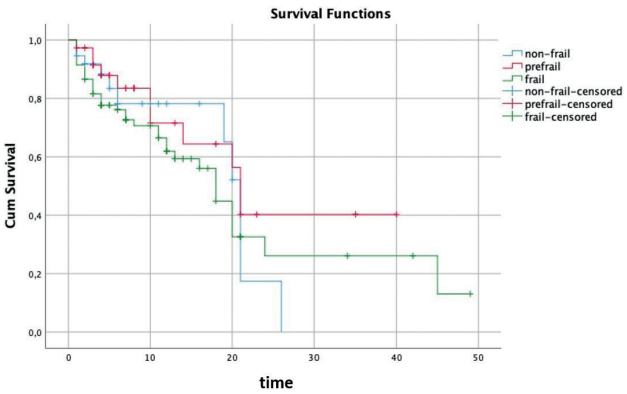

Figure 1. Mortality rates between groups

Table 3. Results of Cox regression analysis

Parameters	Sig.	Hazard ratio	95,0% CI
Age (80-89) (90-99)	0.029	2.233	1.088-4.585
Pressure injury	0.003	2.682	1.384-5.198
APACHE II	0.004	1.112	1.035-1.194
Acute kidney injury	0.023	2.443	1.132-5.270
CFS	0.004	1.256	1.076-1.466

CFS: Clinical Frailty Scale

DISCUSSION

The current study indicated that a higher CFS is linked to an increased risk of mortality, despite the lack of a statistically significant difference in ICU mortality rates among non-frail, pre-frail, and frail patients. Furthermore, we found a significant relationship between age, pressure injury, high APACHE II score, concurrent AKI, and mortality.

Frailty is a clinical condition that refers to an increased vulnerability to external stressors, which is determined by age, comorbidities, and environmental and genetic factors [21]. While age is an important component of frailty, frailty is associated with increased mortality independent of age [22,23]. It is well known that the ICU population contains many frail patients, or frail patients are more prone to being hospitalized in the ICU. A comprehensive systemic review analyzing 10 observational studies noted that approximately 30% of individuals admitted to the ICU were frail [24]. Considering the relationship between age and frailty, it is expected that the likelihood of admission to ICUs will increase in individuals over the age of 80. Indeed, in a multicenter cohort study by Muessig et al. involving octogenarian patients, it was observed that 53.6% of those in intensive care were frail [17]. Similarly, Bruno and colleagues reported that 42% of octogenarians and 58% of nonagenarians (≥90 years old) were frail in the ICU [25]. In the same way, 52.5% of the patients were frail, and 23.7% were pre-frail in our study.

It is vital to know how we measure frailty severity and outcomes, in addition to knowing that frail elderly patients are more likely to be in the ICU. The CFS is a user-friendly instrument for routine application that offers vital insights into the mortality risk of patients in the ICU. De Geer et al. indicated that frailty is a reliable indicator of 30-day mortality (hazard ratio: 2.12) in unselected ICU patients. A multicenter study including 308 patients revealed that an increase in CFS was associated with a risk of 30-day mortality (OR: 1.44 per point increase) [17]. They also reported a 17.3% in-ICU rate that was significantly lower than ours (37.2%). This reduction may be due to the inclusion of planned postoperative admissions to the ICU following elective surgeries with low death rates. Despite our emphasis on lower mortality rates in postoperative patients, it was demonstrated that discharge rates are lower in frail octogenarians compared to their non-frail counterparts admitted to the ICU following surgery [26]. From this perspective, physicians should be aware of their patients' frailty regardless of the reason for admission to the ICU. To us, one additional potential cause of higher mortality in our study population may be the absence of hospices in our country, which contributes to the majority of deaths occurring in ICUs. A study examining the places of death among patients with respiratory diseases, predominantly elderly individuals, indicated that an increase in the number of nursing homes or facilities correlated with a decrease in hospital deaths over time [27]. Moreover, although individuals showing increased frailty face a greater mortality risk, the absence of significant differences across groups may be attributed to the limited sample size and the unequal distribution among the groups.

The APACHE II score is a widely used tool to determine mortality in both young and old individuals in the ICU [28]. The higher the APACHE II score, the higher the mortality. In our study, the average APACHE II score was 18, which corresponds to approximately a 25% risk of death [29]. The APACHE II score was significantly higher in the frail group compared to the non-frail group in our study. Consistent with our findings, Kalaiselvan and colleagues reported that frail patients had higher APACHE II scores in their study that included people aged 50 and beyond [23]. Similarly, it was shown that there is a correlation between frailty and the APACHE II score in elderly patients admitted to

ICU following surgery [30]. Considering that the APACHE II score requires extensive data, including detailed laboratory results, the assessment of frailty using CFS can provide clinicians with an effortless and quick assessment.

The common comorbidities among geriatric patients include diabetes mellitus (DM), hypertension, chronic obstructive pulmonary disease (COPD), cancer, and dementia [31]. Similar to existing literature, hypertension, DM, and coronary artery disease were the leading comorbidities, followed by cancer, COPD, and dementia in our study. In addition, comparative analysis between groups revealed that the frail group had a significantly higher prevalence of dementia, cerebrovascular disease, and malignancy. This increase may be due to dementia and cerebrovascular diseases causing mobility issues, as well as cancer inducing fatigue and weight loss [32,33]. Additionally, we also recorded the acute illnesses detected during the ICU stay. In our study group, the most frequent acute problems detected during ICU stay were infections, AKI, and acute respiratory failure, respectively. Further analysis revealed that AKI and cardiovascular diseases are significantly more common in the frail group. Given that the majority of patients have multiple comorbidities, it is arguably unsurprising that they experience numerous acute issues throughout their ICU stay. Also, these issues are known to worsen each other during or after hospitalization. In line with our data, a recent comprehensive review reported that hypertension, coronary artery disease, heart failure, and DM are the most common disorders, and the majority of patients face acute problems, including cardiovascular, renal, and respiratory complications and infections [34].

Acute respiratory failure is a common problem during ICU stays. Laporte et al. indicated that the number of elderly patients admitted to the ICU for acute respiratory failure has risen over the years [35]. De Lange and colleagues observed that 50% of their octogenarian patients were intubated during their ICU stay, and 7% underwent tracheostomy. In another cohort of 1,220 patients aged 80 years and older, 5.9% of patients admitted to ICU for respiratory failure required invasive mechanical ventilation, whereas 29.1% required non-invasive mechanical ventilation [36]. Approximately fifty percent of our patients needed invasive mechanical ventilation, with 11.8% successfully extubated and 11.8% undergoing tracheostomy. Differences in intubation rates may be attributed to variations in patient characteristics and variances among clinics about intubation and end-of-life decisions.

A significant limitation of our study was the small number of patients, which restricts its generalizability to the general population. The retrospective design resulted in some limitations, such as the inability to include comprehensive geriatric assessments in the study. Additionally, since the frailty assessment was performed by only one researcher, there may be potential bias in it due to a lack of data on inter-rater reliability. On the other hand, the inclusion of real-life data from unselected intensive care patients strengthened our study. Furthermore, there is very little research about octogenarians in the literature, so we believe that this study will make a significant contribution to readers' knowledge.

In conclusion, frailty assessment provides critical insights on elderly patients admitted to the ICU. The association with the APACHE II score and its predictive capacity for death make CFS a rational alternative instrument in routine ICU practice.

Author contribution

Study conception and design: AMK, PU; data collection: AMK; analysis and interpretation of results: AMK and PU; draft manuscript preparation: AMK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the ethics committee for clinical research of Ministry of Health, Etlik City Hospital, Ankara, Türkiye. (AESH-EK1-2023-764/27.12.2023).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Testicular prostheses: effects on sensual confidence

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ABSTRACT

Objective: Testicular implants were presented to improve impaired physical self-confidence of the patients due to lack of testicles. The evaluation of the pediatric population who underwent gonadectomies with or without testicular prostheses placement has not been sufficient so far regarding body image perception, psycho-social interactions with their peers, male friends, and intimate partners through distinctive functional stages in their lifespans. With this study, we aimed to reveal and analyze the experiences of our patients with testicular implants in terms of self-esteem, concerns and complaints during their social and sexual interactions across the passage from childhood to adulthood.

Materials and Methods: The medical records of the pediatric patients who underwent testicular prostheses insertion were examined retrospectively. The questionnaire titled "The Physical and Emotional Evaluation of Testicular Prosthesis Implanted Patients" was sent to each patient and completed surveys were received by post.

Results: Eleven pediatric patients received 18 testicular prostheses. The median age of the patients at time of the procedures was 17 years old. Eight of the patients accepted to participate the study and completed the questionnaire. All patients agreed that chance of providing the normal appearance of scrotum was important. Four patients found their prostheses improper compared to normal ones. Two patients expressed discomfort during their sexual experiences which resulted in shame in one and no effect in the other patient.

Conclusions: Emotional status of the children with testicular prostheses needs to be studied separately and in a more detailed way according to their different developmental stages. The necessary support that would be given by child and adolescent psychiatrists before and after the implantation may improve the psycho-social status of the patients. The patients and their families should be informed properly about the advantages and probable early and late psycho-social consequences of the implants.

Keywords: orchiectomy, testicular prosthesis, children, self-esteem, sexual health

INTRODUCTION

Testicular implants were introduced to improve impaired physical self-confidence of the patients due to lack of testicles following gonadectomy operations. Absence of the testicles may disrupt the body image perception of the school age boys among their peers and furthermore may cause psycho-social problems in social interactions and intimate relationships with their male friends and sexual partners especially throughout adolescence and young adulthood period [1-4]. However, placement of an artificial object might result in good or bad consequences with the start of sexual life of the recipients despite having aesthetical enhancement.

Quite adequate data is present regarding the patients who had their orchidectomies and testicular implants in adulthood period reporting good implications on body image perception and self-confidence, and no undesirable effects on their sexual interactions [5-7]. Unfortunately, children who underwent testicular prostheses insertion succeeding gonadectomies due to cryptorchidism, testicular torsion and atrophy, gender re-assignment surgeries in congenital disorders, malignancy and trauma have not been evaluated sufficiently considering likewise impending future problems until recent period. Appreciatively, we have been able to receive some data about patients' concerns and complaints during the transition period from childhood to adulthood in the light of current studies [8,9]. These studies would help recognition of the deficiencies that we can improve through our practices to create more comfortable lifetime for this very specific group of patients.

With this single center study that we previously shared technical details of our testicular prostheses implanted children, we aimed to reveal and analyze the experiences of the study group in terms of self-esteem, concerns and complaints during their social and sexual interactions across the passage from childhood to adulthood [10].

MATERIAL AND METHODS

The medical records of the patients who underwent testicular prostheses insertion were examined retrospectively. The questionnaire titled "The Physical and Emotional Evaluation of Testicular Prosthesis Implanted Patients" was sent to each patient by post. The patients and/or their parents/guardians who signed the informed consent form completed the questionnaire and sent them back.

This study was approved with application number of 410.01-3287 by Ethics Commission of Hacettepe University.

RESULTS

Eleven pediatric patients received 18 testicular prostheses between 2000 and 2010 at the Pediatric Surgery Department of Hacettepe University Hospital. The median age of the patients at time of the procedures was 17 years old (range: 12-20 years). Gonadectomy indications were bilateral testicular atrophy (n=3), testicular torsion (n=3), female pseudo-hermaphroditism (n=2), mixed gonadal dysgenesis (n=1), unilateral testicular atrophy (n=1), and endodermal sinus tumor (n=1). Bilateral implants were placed in 6 patients and one patient received a third implant with the need of a revision. Silicone gel-filled (n=6) and saline-filled (n=5) testicular implants were used regarding the material of the implants, and there was no information available for 7 prostheses.

Eight of the patients accepted to participate in the study and completed the questionnaire. The age distribution of the patients when they fill in the questionnaire was <15 years old (n=2), 15-24 years old (n=5), and 25-34 years old (n=1). All patients agreed that the chance of providing a normal appearance of their scrotum was important. Four patients denoted that they found their prostheses inappropriate. One patient stated that his prosthesis was harder, smaller, rounder, and more inferiorly located than normal testis. Other patients reported that their prostheses were harder and smaller (n=1), harder and bigger (n=1), and harder (n=1) compared to normal ones (Table 1).

Seven patients including three cases who thought that they had unsuitable prostheses expressed their overall contentment and found implantation advisable for the similar patients. They phrased that they would like to have new prostheses in case of any implant damage.

Two of the patients were sexually active. One of them affirmed no problem derived from the implant during his sexual activity even though he thought that his implant was smaller and harder compared to his normal testis. The other patient expressed his sense of shame about his smaller, harder, inferiorly located and round shaped prosthesis during his sexual experience.

The questions included in the questionnaire and distribution of the answers are listed at Table 2.

DISCUSSION

The absence of the testicles for males has been considered as mirroring of the absence of the breasts or uterus in females [11]. Testicular and breast implants were presented in the context of the necessity to improve self-confidence of this group of patients about their physical appearance. Although both genders are affected profoundly by the disrupted body image and/or fertility concerns, the male side of the story has not been evaluated detailed enough. Furthermore, the present limited literature related to the male gender predominantly covers the adult patients or examine the child, adolescent and adult patients altogether [2-8,11-23]. The assessment of the pediatric population who underwent gonadectomies with or without testicular prostheses placement starting from very early ages has not been sufficient so far regarding body image perception, patients' relationship with their peers, male friends and intimate partners passing through distinctive functional stages in their lifespans. Undeniably, the overlooked sufferings of these patients with the lack of knowledge might cause inferiority complex and social isolation resulting from impaired body image perception and subsequently might interrupt the critical physical, psychological and sexual developmental phases by aging [14-16].

The overall complaints of the patients with testicular prostheses can be listed as inappropriate size, shape, firmness, weight, feeling cold to touch, chronic pain, positioning superiorly or inferiorly, and fixed status/immobility of the implants compared to the present or observed normal testis. The stiffness of the implants has been described as the most frequent problem which was too firm to touch [1,3-9,11,12,14,16]. Araújo et al. reported that 96.1% of their patients felt comfortable with their implants according to the analysis of 51 patients including mostly adults. Additionally, 94.1% of those patients stated that they would have the same surgery in case any damage happens to their implants [8]. Studies have revealed that gonadectomy patients with implants showed better confidence in their intimate relationships and about changing their clothes in the public places despite no statistical significance in comparison to gonadectomy patients without prostheses [1,8,12,21,22]. Four of the patients in our study complained about their prostheses as being harder, smaller, bigger, rounder in shape and positioning too much inferiorly compared to their normal testes. Seven out of 8 patients in our study involving three cases with complaints expressed overall satisfaction about their prostheses and found implantation advisable for the similar patients. They also affirmed that they would like to have new prostheses in case of any complications which conclude with implant removal. Consistent with the several readings, the material used in the production of the implants either being silicone gel-filled or serum saline-filled did not make any impact addressing the cause of the complaints in our limited experience [1,8,12,13,20-24].

According to the literature, adolescent, young adult and adult patients have also specified intense anxiety before and during their sexual intercourses especially at time of the first experience [7,12,15,18-19]. Zilberman et al. reported no sexual interaction related problems with the questionnaire applied on 19 pediatric and adult patients with testicular

Table 1. Patients with complaints about their testicular prostheses

Patient	Complaints	Implant type	Unilateral/Bilateral implants	Sexual life
1	Harder, smaller, rounder, more inferiorly located compared to his other testis	Serum saline-filled	Unilateral	Sexually active with low self-esteem
2	Harder, smaller compared to his other testis	Serum saline-filled	Unilateral	Sexually active with confidence
3	Harder, larger compared to his other testis	Silicone gel-filled	Unilateral	-
4	Harder compared to his other testis	Silicone gel-filled	Unilateral	-

Table 2. The questionnaire and the distribution of the answers.

Questions		Answers	Results		
			a	b	c
1	How did you decide for prosthesis implantation?	a – my own decision b – by help of my family	4	4	
2	Is it important for you to have a physical appearance with 2 testicles?	a – very important b – important c – not important	5	3	
3	Do you think it is important to know the chance of having testicular prosthesis insertion after gonadectomy?	a – yes b – no	8		
4	Does your prosthesis disturb you physically?	a – yes b – no	2	6	
5	Please describe your thoughts about your prosthesis.				
	A. About Size	a – too small b – normal c – too big	2	5	1
	B. About Weight	a – too light b – normal c – too heavy		8	
	C. About Shape	a – normal b – abnormal	6	2	
	D. About Position	a – normal b – abnormal	5	3	
	E. About Consistency	a – normal b – abnormal	4	4	
6	Is there any change in your feelings about your body image after prosthesis insertion?	a – I feel extremely better b – I feel better c – no change	2	2	4
7	Is there any change about your self-confidence after prosthesis insertion?	a – I feel extremely more confident b – I feel confident c – no change	2	1	5
8	How do you feel being in public baths?	a – no problem b – No problem if I change my clothes in another room c – I feel uncomfortable and do not go such places.	4	1	3
9	How do you feel around females?	a – no problem b – I usually abstain from close contacts c – I feel uncomfortable	4	1	3
10	Have you ever had sexual relationship?	a – yes b – no	2	6	
11	Have you experienced any problem about your prosthesis during sexual relationship?	a – yes b – no	1	1	
12	Do you feel comfortable with your decision of prosthesis insertion?	a – yes b – no	7	1	
13	Do you advise testicular prosthesis insertion to the patients with the similar problems?	a – yes b – no	8		
14	Would you want reimplantation if any harm happens to your prosthesis that would cause removal of it?	a – yes b – no	8		

implants [1]. Araújo et al., Catanzariti et al. and Turek et al. reported no erectile dysfunction in the presence of the prostheses [8,19,22]. Researchers also surveyed the association between the motivation to receive an implant and the status of marriage or steady intimate relationship and found controversial results such as less determination or no influence [8,9,13,20,25]. Two of our patients expressed discomfort during their sexual experiences thinking about their unfitting implants which resulted in shame in one and no effect in the other patient.

Chantzi et al. reported supportive data to the current literature in their recent article including number of 16 pediatric patients with testicular prostheses and emphasized the importance of the problems that might occur during adolescence and young adulthood with the start of intimate relationships. The authors underlined the requirement of analyses made by validated questionnaires in the assessment of these patients stating their study's weakness as using the one prepared by the research team [9]. We also think that it is one of the limitations of our study that we conducted our own questionnaire which was specifically prepared for this research besides our small sized study group. Undoubtfully, surveying with the validated questionnaires for psychological and sexual problems is the best way of scientific practice and enables the homogenization, combination and comparison of the limited data coming from different study groups to achieve more precise outcomes with large number of patients.

Testicular prosthesis insertion requires attention regarding lifelong functional effects on psycho-social and sexual interactions of the recipients but a standard procedure with possible surgical complications. Pediatric patients and their caregivers should be informed properly in a detailed and age specific manner. Demonstration of an implant sample prior to the operation would help significantly for the realistic expectations of the patients in terms features of the implants with the sense of touch [9,13,15]. Patients with the prostheses which were inserted in their early childhood necessitate regular controls consistent with their significant physical, psychological and sexual developmental stages to cover the demand of support needed. A special consideration should be given, and availability of an expert assistance should be offered throughout the transition period of these patients from childhood to adulthood. None of the patients in this study searched for psychiatric support but stated that they wish they were informed more precisely pre- and post-operatively and be followed more frequently in the long-term period.

CONCLUSIONS

There is not enough data about psycho-social status of the patients before and after testicular implantation to assess the short and long-term effects of the prostheses. Emotional status of the children with testicular prostheses needs to be studied in a more detailed way and separately from the adult patients according to their different developmental stages. The necessary support that would be given by child and adolescent psychiatrists before and after the implantation may improve psycho-social status of the patients with a plan of testicular prosthesis insertion. The patients and their families should be informed properly about the advantages and probable early and late sensual consequences of the testicular prosthesis implantation.

Author contribution

Study conception and design: NÇ; data collection: NÇ; analysis and interpretation of results: NÇ; draft manuscript preparation: NÇ, MEŞ and SE. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Ethics Commission (Protocol no. 410.01-3287/29.12.2010).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Age, fracture severity, injury mechanisms and concomitant injuries predict surgical intervention in pediatric proximal humerus fractures

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ABSTRACT

Objective: Proximal humerus fractures (PHFs) in children often heal well with conservative treatment due to the region's high remodeling potential. However, the decision to operate becomes more nuanced in older children or those with severe fracture displacement or high-energy trauma. This study aimed to identify factors associated with operative management of pediatric PHFs.

Materials and Methods: We retrospectively reviewed 41 pediatric patients (aged 6–16 years) with PHFs treated between 2014 and 2024. Patient demographics, Neer-Horowitz classification, injury mechanisms, and presence of concomitant injuries were analyzed. Injury mechanisms were categorized as low-energy or high-energy. Outcomes were assessed using the Pediatric/Adolescent Shoulder Survey (PASS) at final follow-up. Multivariate logistic regression was used to identify independent predictors of surgical treatment.

Results: Of the 41 patients, 19 (46.3%) underwent surgical fixation, while 22 (53.7%) were treated nonoperatively. Patients in the operative group were older (mean 13.2 vs. 10.7 years, $p < 0.001$) and more likely to have Neer-Horowitz Grade III or IV fractures (89.5% vs. 40.0%, $p < 0.001$). High-energy trauma (94.7% vs. 59.1%, $p = 0.003$) and concomitant injuries (52.6% vs. 27.3%, $p = 0.001$) were significantly more frequent in the surgical group. On multivariate analysis, independent predictors of surgery included older age (OR 1.49, $p = 0.018$), Grade III/IV fractures (OR 5.41, $p = 0.015$), high-energy trauma (OR 4.57, $p = 0.040$), and concomitant fractures (OR 5.13, $p = 0.042$). At final follow-up, there was no significant difference in PASS scores between groups (operative: 87.8, nonoperative: 88.9; $p = 0.68$).

Conclusion: Age, fracture severity, high-energy trauma, and concomitant injuries are significant predictors of surgical intervention in pediatric PHFs. However, both surgical and nonoperative treatments yielded excellent functional outcomes, highlighting the importance of individualized treatment strategy.

Keywords: pediatric proximal humerus fracture, surgical indications, Neer-Horowitz classification, high-energy trauma, functional outcomes

INTRODUCTION

Pediatric proximal humerus fractures are relatively uncommon, accounting for approximately 2–5% of all pediatric fractures [1-4]. The proximal humeral physis contributes nearly 80% of humeral growth, giving these fractures excellent remodeling capacity, especially in younger children [5]. As a result, minimally displaced fractures in younger patients are typically managed nonoperatively with excellent outcomes [2]. However, treatment decisions become more complex in older children, adolescents, and cases with substantial displacement or associated injuries [4,5].

There is ongoing debate regarding the appropriate indications for surgical treatment in this population [1,6]. Several classification systems have been proposed to guide treatment, with the Neer-Horowitz classification being one of the most widely used. While higher grades in this system are generally associated with a greater likelihood of operative intervention, clinical decisions often rely on a combination of factors; including patient age, fracture displacement, injury mechanism, and the presence of concomitant injuries. Despite this, few studies have comprehensively evaluated the interplay of these factors in predicting surgical management [7].

Moreover, children presenting with polytrauma or high-energy mechanisms may undergo surgery for other injuries, during which the proximal humerus fracture is addressed as part of the overall treatment strategy. This raises important questions about whether surgical management is always driven by the characteristics of the humerus fracture itself or whether trauma severity plays a significant role. Understanding the clinical, radiographic, and injury-related factors that influence treatment decisions is essential for developing consistent guidelines and avoiding unnecessary surgery in children who are expected to achieve good outcomes with conservative care [1,2,4,8].

The aim of this study was to evaluate the association of age, Neer-Horowitz classification, injury mechanism, and presence of associated injuries with operative management in pediatric PHF. We hypothesized that older age, higher fracture grades, high-energy trauma, and concomitant injuries would be significantly associated with surgical intervention.

MATERIALS AND METHODS

Study design and patient selection

Ethical approval for this study was obtained from the Hacettepe University Faculty of Medicine Local Ethics Committee (Protocol no. SBA 25-618). This retrospective study included pediatric patients with PHF who were treated at a tertiary referral center between January 2014 and December 2024. Eligible patients were identified through institutional databases using diagnostic codes and confirmed via radiographic review. Inclusion criteria were radiographically confirmed PHF, age between 6 and 16 years at the time of injury, and a minimum clinical follow-up of 12 months. Patients with pathological fractures, skeletal dysplasia, or incomplete clinical or radiographic documentation were excluded.

Demographic and injury-related variables were collected including age, sex, side of injury, trauma mechanism, presence of concomitant injuries, and fracture classification. Injury mechanisms were categorized based on clinical documentation and patient history. Low-energy trauma included ground-level falls during routine daily activity. High-energy trauma included high falls (e.g., from stairs, playgrounds, or rooftops) and motor vehicle accidents, both in-vehicle and out-of-vehicle traffic accidents. For statistical analysis, injury mechanisms were grouped into two categories, low-energy and high-energy trauma, to evaluate their association with the likelihood of surgical intervention. Associated injuries were defined as any concomitant musculoskeletal, neurological, or visceral injury diagnosed at presentation. Fracture severity was graded using the Neer-Horowitz classification, based on radiographic displacement.

Treatment approach

Patients were managed either conservatively or operatively based on fracture characteristics, patient age, and overall clinical condition. Conservative treatment was preferred for younger patients, minimally displaced fractures and patients whose condition was not suitable for surgery. It consisted of immobilization with a sling or shoulder orthosis, followed by gradual return to activity with physical therapy as needed (Figure 1). Operative treatment was preferred for older patients, displaced and angulated fractures, open injuries, patients with neurovascular compromise

and polytrauma patients. It was performed under general anesthesia and involved closed or open reduction and percutaneous fixation with K-wires (Figure 2). Surgery was also considered if the patient had a concomitant fracture that required surgical fixation.

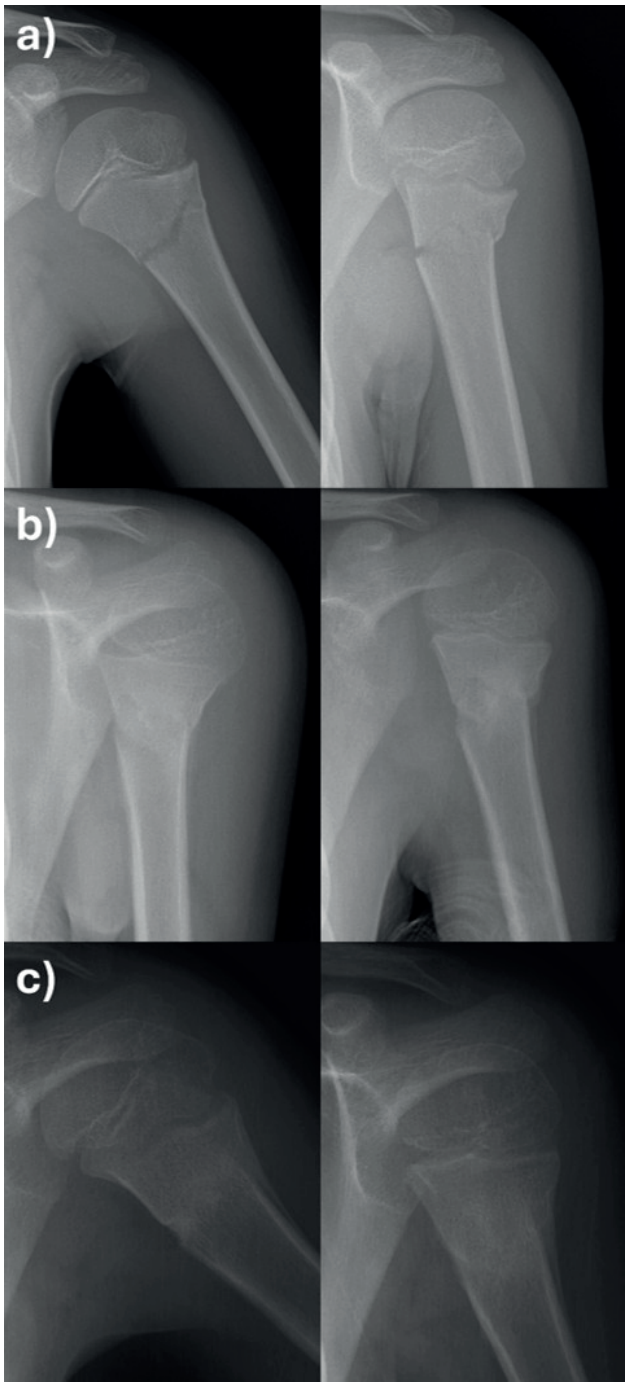

Figure 1. Radiographs of a 7-year-old. Left proximal humerus fracture after falling while playing

(a) Initial anteroposterior and lateral radiographs at the emergency department showing a minimally displaced proximal humerus fracture. The patient was treated conservatively with a Velpeau bandage.
(b) Follow-up radiographs at 3 weeks demonstrating early callus formation.
(c) Follow-up radiographs at 6 weeks showing abundant callus formation with remodeling.

Outcome assessment

Radiographic follow-up was performed at 2-week intervals until 6 weeks post-injury. In operatively treated patients, K-wires were removed at the 6th week, following confirmation of radiographic union. After this period, monthly radiographs were obtained until complete healing was confirmed. Clinical evaluation included range of motion and physical examination at each follow-up visit. Functional outcomes were assessed using the Pediatric/Adolescent Shoulder Survey (PASS) at the final follow-up visits [9].

Statistical analysis

Descriptive statistics were used to summarize the study population. Categorical variables were compared using chi-square or Fisher's exact tests, and continuous variables were analyzed using independent samples t-tests or Mann–Whitney U tests, depending on data distribution. Multivariable logistic regression analysis was performed to evaluate the association between operative management and variables including age, sex, fracture classification, injury mechanism, and presence of associated injuries. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY).

RESULTS

A total of 41 pediatric patients with PHF were included in the study. The mean age at injury was 11.5 ± 2.6 years (range, 6–16 years), and 25 patients (61.0%) were male. The dominant side was affected in 22 patients (53.7%). The mean duration of clinical follow-up was 26.7 ± 13.2 months (range, 12–60 months). Injury mechanisms were categorized as high-energy trauma in 31 patients (75.6%), which included motor vehicle accidents both out-of-vehicle ($n = 16$) and in-vehicle ($n = 9$) as well as high falls ($n = 6$). Low-energy falls were observed in 10 patients (24.3%) (Table 1). Concomitant injuries were present in 16 patients (39.0%), most commonly involving the tibia ($n = 10$), forearm ($n = 4$), or femur ($n = 2$) (Table 2). Nine of these patients underwent additional surgical procedures in the same session as proximal humerus fixation.

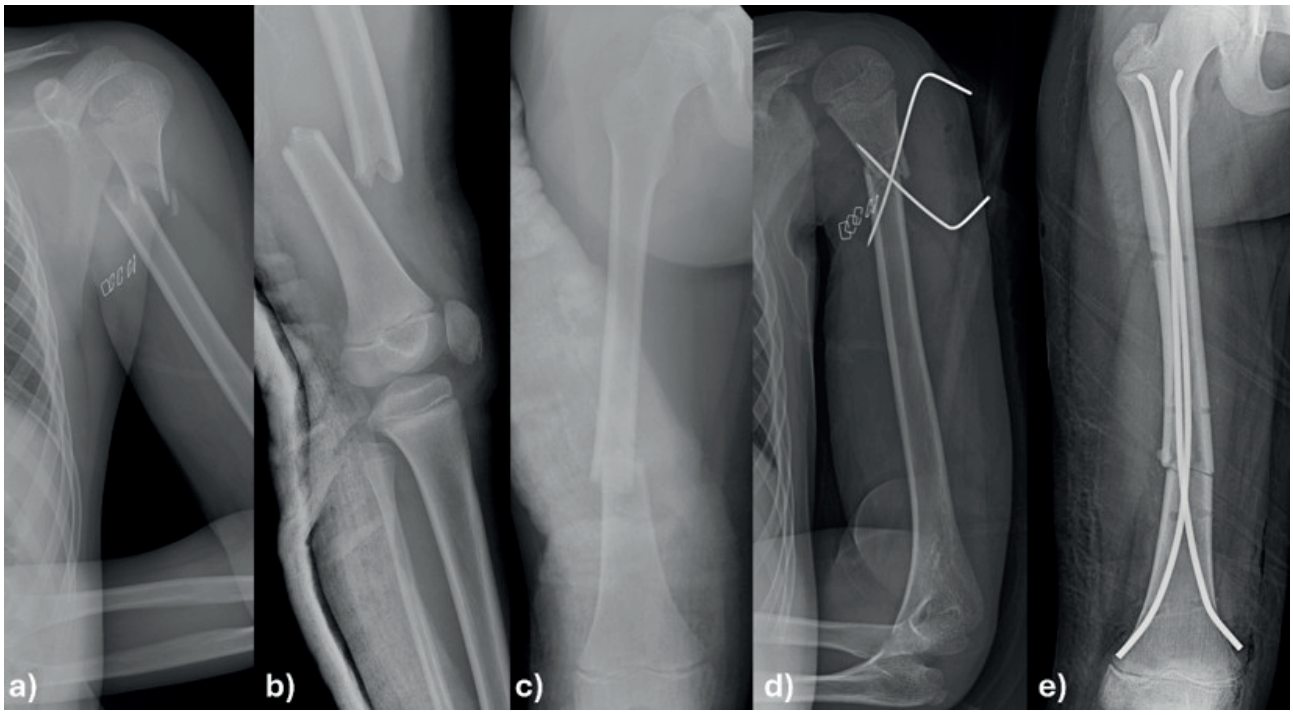

Figure 2. Radiographs of a 12-year-old male polytrauma patient following a traffic accident, referred intubated from a level 1 hospital

(a) Initial right shoulder radiograph showing displaced proximal humerus fracture.

(b, c) Initial right lower extremity radiographs demonstrating displaced distal femoral fracture.

(d) Postoperative right shoulder radiograph after closed reduction and percutaneous fixation with crossed K-wires.

(e) Postoperative right femur radiograph after closed reduction and stabilization with titanium elastic nails.

Table 1. Patient demographics and Injury characteristics

Variable	Operative (n=19)	Nonoperative (n=22)	Total (n=41)	p-value
Age (years), mean ± SD	13.2 ± 1.6	10.7 ± 2.6	11.5 ± 2.6	**<0.001**
Sex (male), n (%)	12 (63.2%)	13 (59.1%)	25 (61.0%)	0.79
Dominant side affected, n (%)	11 (57.9%)	11 (50.0%)	22 (53.7%)	0.62
Concomitant injuries, n (%)	10 (52.6%)	6 (27.3%)	16 (39.0%)	**0.001**
High-energy trauma, n (%)	18 (94.7%)	13 (59.1%)	31 (75.6%)	**0.003**

According to the Neer-Horowitz classification, 5 patients (12.2%) had Grade I fractures, 10 (24.4%) had Grade II, 11 (26.8%) had Grade III, and 15 (36.6%) had Grade IV fractures. Operative treatment was performed in 19 patients (46.3%), while 22 patients (53.7%) were managed nonoperatively (Table 3).

The mean age was 12.4 ± 3.33 among patients with Grade IV fractures (n=15), and 7 of them were male. Nine of them had concomitant fractures, and 11 of them sustained high-energy traumas. Patients whose condition was not suitable for surgery, younger patients' fractures with acceptable alignment after closed reduction and low-energy fractures with less soft tissue damage were treated conservatively.

Among surgically treated patients, 17 (89.5%) had Grade III or IV fractures, while only 2 (10.5%) had Grade I or II fractures. Seven patients underwent humerus fixation during surgery for other concomitant fractures.

Clinical outcomes

At final follow-up, the mean PASS score was 88.4 ± 9.1 in the entire cohort. The operative group had a mean PASS score of 87.8 ± 9.5, while the nonoperative group scored 88.9 ± 8.8, with no statistically significant difference between groups ($p = 0.68$). All patients achieved fracture union, and there were no reports of growth disturbances, osteonecrosis, or major complications.

Table 2. Associated fractures

Concomitant Fracture Type	Operative (n)	Nonoperative (n)	Total (n)
Tibia	8	2	10
Forearm	2	2	4
Femur	2	0	2

Table 3. Fracture Severity by Neer-Horowitz Classification

Neer-Horowitz Grade	Operative (n=19)	Nonoperative (n=22)	Total (n=41)	p-value
Grade I	0 (0%)	5 (22.7%)	5 (12.2%)	**<0.001**
Grade II	2 (10.5%)	8 (36.4%)	10 (24.4%)	
Grade III	6 (31.6%)	5 (22.7%)	11 (26.8%)	
Grade IV	11 (57.9%)	4 (18.2%)	15 (36.6%)	

Predictors of surgical intervention

Older age was significantly associated with surgical intervention, with operatively treated patients having a mean age of 13.2 years compared to 10.7 years in the nonoperative group ($p < 0.001$). Higher Neer-Horowitz fracture grades were also significantly associated with surgery, as 92.3% of patients in the operative group had Grade III or IV fractures, compared to 40.0% in the nonoperative group ($p < 0.001$). High-energy trauma mechanisms were more common in the surgical group (69.2%) than in the nonoperative group (25.7%), demonstrating a significant association ($p = 0.003$). Furthermore, the presence of concomitant fractures significantly increased the likelihood of operative management, occurring in 53.8% of surgically treated patients compared to 11.4% of nonoperative cases ($p = 0.001$). Multivariate logistic regression confirmed that older age (OR 1.49; 95% CI 1.07–2.07; $p = 0.018$), higher Neer-Horowitz grade (OR 5.41; 95% CI 1.38–21.1; $p = 0.015$), high-energy mechanism (OR 4.57; 95% CI 1.07–19.4; $p = 0.040$), and concomitant fractures (OR 5.13; 95% CI 1.06–24.9; $p = 0.042$) were all independently associated with operative treatment (Table 4).

DISCUSSION

This study identified age, fracture severity, high-energy trauma, and concomitant injuries as significant predictors of surgical intervention in pediatric PHFs. Although nearly half the patients underwent operative management, functional outcomes were excellent across both groups, demonstrating the high remodeling potential and favorable prognosis of these injuries in skeletally immature individuals.

Age has long been established as a critical factor in treatment decisions for PHFs due to the remodeling capacity of the proximal humeral physis, which contributes approximately 80% of the humerus's longitudinal growth [2,5]. Younger children typically recover well even from moderately displaced fractures, while older children and adolescents are more likely to require surgical correction due to decreased remodeling potential [5]. In our cohort, this age-dependent trend was clearly evident and supports the threshold proposed by Lefèvre et al., who suggested considering surgery in children older than 11 years with significant displacement [5].

Table 4. Multivariate logistic regression analysis

Variable	Odds Ratio (OR)	95% Confidence Interval	p-value
Age (per year increase)	1.49	1.07 – 2.07	**0.018**
Neer-Horowitz Grade III/IV	5.41	1.38 – 21.1	**0.015**
High-energy trauma	4.57	1.07 – 19.4	**0.040**
Concomitant fracture	5.13	1.06 – 24.9	**0.042**

Fracture severity also played a major role, with Grade III–IV fractures significantly associated with surgical treatment. This finding is consistent with prior studies demonstrating that more displaced fractures are less likely to remodel acceptably and therefore carry a higher likelihood of operative management [1,6,7]. Our results align with Karagöz et al. who also reported higher surgical rates in patients with Neer-Horowitz Grades III and IV [7]. While conservative management is the standard approach for Grade I-II fractures, two patients with Grade 2 fractures underwent surgery. These decisions were influenced by concomitant injuries requiring surgical intervention, persistent severe pain, poor patient adherence to conservative treatment plans, and unsuccessful closed reduction attempts. While these fractures show good response to conservative approaches, surgical approaches may give better results in selected cases.

In polytrauma cases, the management strategy differed from other patients. The treatment decision was not only influenced by fracture characteristics but also by the need for fixation of other fractures and the overall clinical condition of the patient. Internal fixation of the humerus was performed in the same session if the patient had any fractures that needed surgery. Patients who were in poor systemic condition or had contraindications for surgery were managed conservatively. In our study, seven patients underwent humerus fixation during the surgical session for concomitant fractures, and four patients couldn't be operated on because of their overall condition. These patients were followed at the intensive care unit.

An important finding of our study is the identification of injury mechanism as an independent predictor for the decision to perform surgery. High-energy trauma, such as motor vehicle accidents and high falls, was more prevalent in the operative group and remained a significant factor even after adjusting for age and fracture type. While this association is often acknowledged clinically, it has not been consistently quantified in previous literature. Our findings extend those of Cruz et al., who observed increased surgical intervention in polytrauma cases, suggesting that global injury severity, not just fracture characteristics, can influence treatment decisions [8].

Concomitant injuries were also an important factor influencing the decision of surgical management. In many cases, PHFs were surgically treated during operative treatment of other fractures. This pattern has been noted in other studies, including those by Song et al. and Fiandeiro et al., who emphasized the need to consider broader trauma patterns in pediatric upper extremity injuries [4,9]. Such combined procedures may reflect logistical efficiency and patient safety considerations in polytrauma care, but they also complicate the evaluation of fracture-specific treatment outcomes.

Importantly, our study supports that both surgical and conservative treatment approaches can yield excellent functional recovery when appropriately selected. The lack of difference in PASS scores aligns with the meta-analysis by Song et al., which found no consistent functional advantage for surgery in pediatric PHFs when stratified by age and displacement [4]. This emphasizes the continued relevance of nonoperative care in younger children or those with less severe displacement, particularly in isolated injuries.

Several limitations must be acknowledged. The retrospective design introduces potential selection bias, particularly in surgical decision-making, which may be influenced by individual surgeon preference or institutional protocols. Although we used validated classification systems and functional scores, the assessment of PASS may not fully capture subtle strength or ROM differences. Finally, as a single-center study from a tertiary institution, our results may not generalize to all practice settings, especially those with different surgical thresholds or resource availability.

CONCLUSION

Our findings show that age, fracture severity, high-energy injury mechanism, and concomitant trauma are significant predictors of surgical intervention in pediatric PHFs. Nevertheless, functional outcomes were excellent across both groups, supporting the case-specific approach. These results support existing literature and highlight the importance of considering not only radiographic but also systemic and clinical factors when managing these injuries.

Author contribution

Study conception and design: MK, UCK, SI, OMK, GA and SK; data collection: MK, UCK, SI and OMK;

analysis and interpretation of results: MK, UCK, SI and OMK; draft manuscript preparation: MK, UCK, SI, OMK, GA and SK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Faculty of Medicine Local Ethics Committee (Protocol no. SBA 25-618/08.07.2025).

Funding

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Omentopexy as a novel adjunct to detorsion in ovarian torsion: experimental evidence

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ABSTRACT

Objective: In the treatment of ovarian torsion, the primary goal is to preserve the ovary through detorsion, even when it appears blue-black. However, no routinely applied method currently exists to prevent ischemia-reperfusion (I/R) injury that occurs after detorsion. The aim of this study is to evaluate the effect of wrapping the detorsioned ovary with omentum in preventing I/R associated tissue damage

Materials and Methods: Fifteen Sprague–Dawley rats were randomly assigned to three groups (n = 5 each). In the sham group, laparotomy was performed, and the abdomen was closed without further intervention. In the control group, the left ovary was rotated 720° clockwise and fixed to the anterior abdominal wall, followed by omentectomy. After 24 hours, laparotomy was repeated and the ovary was detorsioned. In the experiment group, the left ovary was rotated 720° clockwise and fixed to the anterior abdominal wall. After 24 hours, laparotomy was repeated, the ovary was detorsioned, and then wrapped in omentum. Twenty-one days after the first surgery, oophorectomy was performed in all groups. Ovarian tissues were histopathologically examined for congestion, interstitial edema, neutrophilic infiltration, and necrosis, and overall tissue damage scores were calculated.

Results: There was no significant difference between the sham and experiment groups regarding overall tissue damage ($p = 0.171$). However, the control group had significantly higher tissue damage compared to the sham group ($p = 0.001$). Necrosis was observed in two ovaries of the control group, whereas no necrosis was seen in the sham or experimental groups. Viable follicles were detected in only two rats in the control group, while all rats had viable follicles in the sham and experiment groups.

Conclusion: Omentopexy was found to be effective in tissue healing. Wrapping the ovary with omentum after detorsion may help preserve ovarian function and maintain follicular viability.

Keywords: omentopexy, ovarian torsion, detorsion, ischemia reperfusion injury

INTRODUCTION

Ovarian torsion is the most frequent gynecologic emergency in children. It accounts for 2.7% of acute abdominal pain cases in children [1]. Historically, oophorectomy was the choice of treatment due to concerns for thromboembolism and malignancy risk [2]. However, studies have demonstrated that there is no increase in the risk of thromboembolism or malignancy after detorsion when compared to oophorectomy as previously supposed [3-5]. Currently, detorsion and preservation of the ovary is the treatment of choice. However, some of the untwisted ovaries vanish after the operation and some fail to have healthy follicles [6]. There is not any clinical, laboratory or image defined study to demonstrate the viability of the untwisted ovary. Even a blue-black appearance of the ovary resembling necrotic tissue does not indicate irreversible damage [7,8].

The tissue damage in the untwisted ovary is secondary to direct damage caused by ischemia itself and reperfusion injury [9,10]. Decreased ovarian circulation due to torsion cause an ischemic damage histologically confirmed with edema, inflammatory infiltration, necrosis, vascular congestion and follicular degeneration. Ovarian blood flow may be only partial or slow after untwisting and ischemic injury can go on. Furthermore, maintaining the circulation after detorsion may cause oxidative stress and worsen the damage leading ischemia/reperfusion (I/R) injury [9,10]. Animal studies demonstrated many effective methods to prevent I/R injury of ovary. However, there is not any clinically proven method to protect the structure and function of the untwisted ovary.

Omentum exerts angiogenic activity in adjacent organs by secreting angiogenic cytokines and accelerates healing in ischemic or inflamed tissue [11]. Surgically approximation of an omentum flap helps revascularization of ischemic tissue [12]. In addition, it is known that omentum helps the perfusion of free tissues such as trachea, small intestine and sciatic nerve grafts [13,14]. Ability of omentum to promote healing and regeneration is clinically used in treatment of traumatic and surgical wounds, restructuring soft tissue defects and in supporting tissue healing [15]. Given the potential healing properties of omentum, we hypothesize that omentopexy can decrease tissue damage and improve recovery after detorsion of the torsed ovary. The aim of this study is to evaluate whether omentopexy decreases ischemic tissue damage and I/R injury of the untwisted ovary in an animal model of ovarian torsion or not.

METHODS AND MATERIAL

The experiment is approved by institutional Animal Experimentations Ethics Board Commission and guidelines for responsible use and animal care were followed strictly.

Animals

Fifteen adult female Sprague Dawley (SD) rats with a mean weight of 220gr (200-250 gr) were used in the study. Animals were fed ad libitum and housed in a temperature-controlled environment (20°C to 22°C) with a relative humidity of 40% to 50% and photoperiod of 12-hours light/12-hours dark. Rats were randomly assigned into three groups: Group I (sham group), Group II (control group) and Group III (experiment group).

Anesthesia

All surgical procedures were performed under general anesthesia. Anesthesia was induced and maintained by intramuscular administration of 10 mg/kg ketamine (Ketalar; Pfizer, İstanbul, Turkey) and 5 mg/kg xylazine (Rhompun; Bayer, İstanbul, Turkey). Rats were maintained on spontaneous respiration throughout the anesthesia. Analgesia was provided with 1mg/mL acetaminophen (Tylol; Nobel İlaç Sanayi ve Ticaret AŞ, İstanbul, Turkey) added to drinking water.

Surgery

All animals were placed in supine position and 4-cm long midline abdominal incision was made under sterile conditions. Mobile viscera were exteriorized within a saline soaked towel.

In group I abdominal wall was closed without any further intervention.

In Group II left ovary was rotated for 720 degrees clockwise and fixed to anterior abdominal wall with 3/0 silk suture (İpek; Doğsan, İstanbul, Turkey).

All the rats in Group II had omentectomy. Twenty-four hours after the first operation left ovary was untwisted and left free in the abdominal cavity.

In group III left ovary was rotated clockwise for 720 degrees and fixed to anterior abdominal wall with 3/0 silk suture (İpek; Doğsan, İstanbul, Turkey). Twenty-four hours after the first operation left ovary was untwisted. The omentum flap was approximated to left ovary. Omentopexy was completed by wrapping the omentum around left ovary.

Twenty-one days after the first operation, all rats underwent laparotomy and left ovaries were removed.

Histopathological evaluations

Tissue samples were rinsed immediately and fixed in 10% formalin at room temperature for 72 hours and were processed according to routine light microscopic tissue processing. They were dehydrated in ascending degrees ethanol, cleared in xylene and embedded in paraffin. Serial sections of 5 µm was cut and stained with H&E. Sections were photographed with Olympus BH2 light microscope (Olympus, Tokyo, Japan).

Tissue samples were evaluated by a single pathologist in a blinded fashion. Congestion, interstitial edema, neutrophilic infiltration, necrosis and presence of viable follicles were noted. Tissue damage was evaluated by semiquantitative scoring of five examined microscopic areas of each specimen. The score of pathological change was 0, 1, 2 and 3; when there was no, mild (<25% of microscopic areas), moderate (25% to 75% of microscopic areas), severe (>75% of microscopic areas) respectively. Total tissue damage was calculated by addition of congestion, interstitial edema, neutrophilic infiltration and necrosis scores.

Statistical analysis

The statistical package SPSS for Windows 21.0 (Statistical Package for Social Sciences; SPSS Inc, Chicago, Illinois) was used to analyze data. Kruskal-Wallis test, Fischer's exact test and Chi-square test were used for analysis. P values less than 0.05 were considered statistically significant.

RESULTS

In group I, specimens of two rats had vascular congestion, and none had interstitial edema, neutrophilic infiltration or necrosis. In group II specimens of all rats had vascular congestion, interstitial edema and neutrophilic infiltration and two rats had necrosis (Figure 1, 2). In group III specimens of all rats had vascular congestion and neutrophilic infiltration, one had interstitial edema, and none had necrosis (Figure 3). There were healthy ovarian follicles in specimens of all rats in group I and III. Specimens of two rats in group II had healthy ovarian follicles. There were statistically significant differences among groups in terms of presence of interstitial edema, neutrophilic infiltration and presence of healthy follicles (Chi-square test, $p<0.05$).

Histopathological examination scores are shown in Table 1.

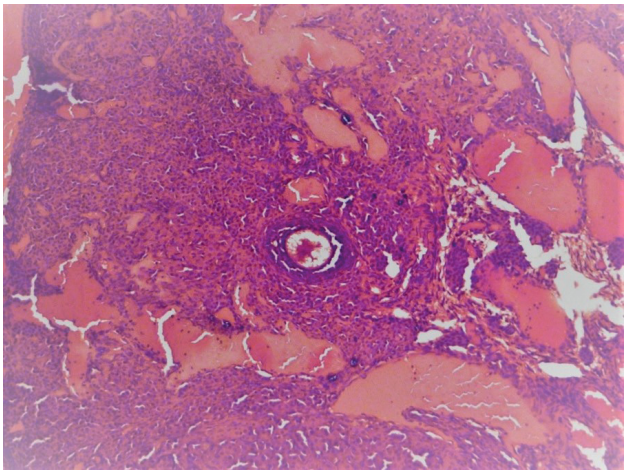

Figure 1. Group II: marked congestion, interstitial edema and neutrophilic infiltration (H&E, x100)

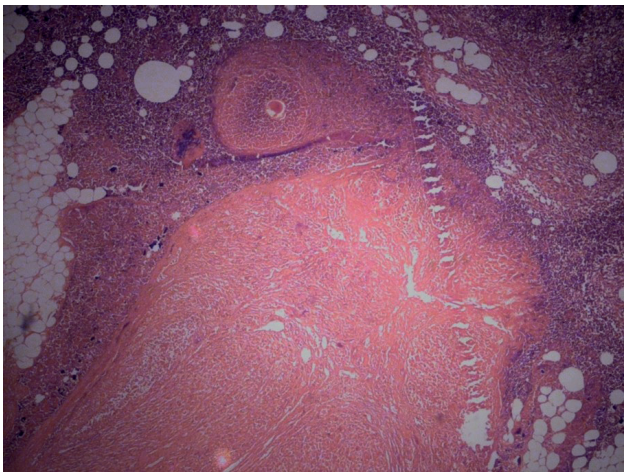

Figure 2. Group II: necrotic ovary (H&E, x100)

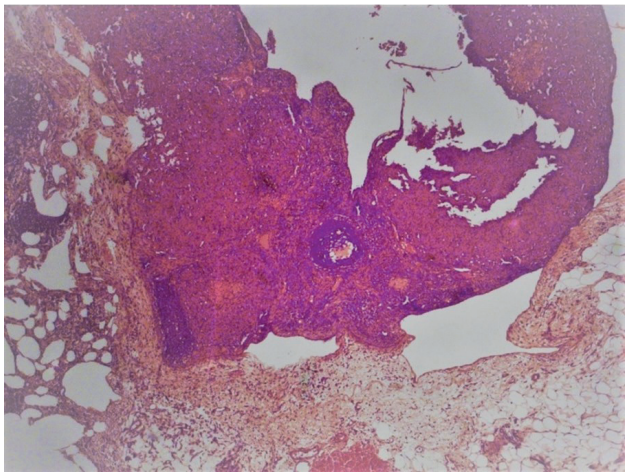

Figure 3. Group III: ovary wrapped with omentum (H&E, x100)

There was statistically significant difference between groups in histopathological scores of interstitial edema and neutrophilic infiltration (Kruskal Wallis, $p<0.05$). In group II, histopathological examination scores of interstitial edema and neutrophilic infiltration were higher than Group I and Group III (Fischer's exact test, $p<0.05$). The interstitial edema and neutrophilic infiltration scores of Groups I and III were not significantly different (Fischer's exact test, $p>0.05$).

Total tissue damage score of Group II was higher than Group I and III (Fischer's exact test, $p<0.05$).

In group II a smaller number of rats had healthy follicle than Group I and III (Fischer's exact test, $p<0.05$). there was not any statistically significant difference between Group I and Group III in terms of presence of healthy follicle (Fischer's exact test, $p>0.05$).

DISCUSSION

Ovarian torsion and it's I/R consequences have been extensively investigated in experimental settings. However, most previous studies employed ischemia durations of only 2-4 hours which may be insufficient to induce significant and reproducible ischemic damage in the ovary [16]. The present study used a 24-hour ischemia model, which resulted in marked histopathological injury, including vascular congestion, interstitial edema, neutrophilic infiltration, necrosis and follicular loss. This prolonged ischemia model therefore provides a more reliable framework to evaluate potential protective strategies.

Restoration of blood flow after detorsion can paradoxically exacerbate ovarian injury through reperfusion mechanisms. Increased production of reactive oxygen species, activation of macrophages and endothelial cells, and neutrophil recruitment contribute to a cascade of inflammatory events.

Table 1. Tissue damage scores

	Vascular Congestion	Interstitial Edema	Neutrophilic Infiltration	Necrosis	Total Tissue Damage
Group Ia	0	0	0	0	0
Group Ib	3	0	0	0	3
Group Ic	3	0	0	0	3
Group Id	0	0	0	0	0
Group Ie	3	0	0	0	3
Group I	**1,8±1,6**	**0±0**	**0±0**	**0±0**	**1,8±1,6**
Group IIa	3	3	3	0	9
Group IIb	3	3	3	3	12
Group IIc	3	3	3	0	9
Group IId	3	3	3	0	9
Group IIe	3	3	3	3	12
Group II	**3±0**	**30**	**3±0**	**1,2±1,6**	**10,2±1,6**
Group IIIa	3	0	1	0	4
Group IIIb	3	0	2	0	5
Group IIIc	3	3	3	0	9
Group IIId	3	0	3	0	6
Group IIIe	3	0	1	0	4
Group III	**3±0**	**0,6±1,3**	**2±1**	**0±0**	**5,6±2**

[17,18]. Activated neutrophils cluster within capillaries, impairing microvascular perfusion and amplifying tissue edema [19]. In turn, cytokines and chemokines perpetuate neutrophil activation and infiltration, sustaining tissue damage and follicular loss [20]. While numerous experimental interventions have been proposed to mitigate I/R injury, no clinically applicable protective method has yet been established.

In the current study, omentopexy significantly attenuated histopathological markers of I/R injury. Interstitial edema and neutrophilic infiltration scores were significantly lower in the omentopexy group compared with the detorsion-only group, while not differing significantly from the sham group. Moreover, the preservation of healthy follicles was markedly higher with omentopexy. Total tissue damage scores were also reduced in the omentopexy group, further supporting protective role.

The beneficial effects of omentum are likely multifactorial. Its rich vascular network and secretion of angiogenic mediators, such as VEGF, promote revascularization. It's lymphatic drainage capacity reduces tissue edema and facilitates clearance of inflammatory mediators. Furthermore, the omentum contains mesenchymal stem cells and immune cell-rich milky spots that release growth factors, chemotactic signals, and progenitor cells to support regeneration of injured tissue [11,18,21]. These mechanisms collectively explain the histopathological improvements observed in the omentopexy group.

Although no statistically significant difference in necrosis was observed among groups, it's noteworthy that all necrotic samples and all specimens without viable follicles were confined to the detorsion-only group. This finding suggests that omentopexy may enhance perfusion and preserve follicular viability, even if the limited sample size precluded statistical significance.

Taken together, this experimental study provides significant preclinical evidence that omentopexy performed on detorsed ovaries reduces ischemia-reperfusion injury and contributes to the preservation of ovarian function. These findings highlight the potential clinical relevance of omentopexy as an adjunct to detorsion in ovarian torsion. Nevertheless, further studies including biochemical markers, functional ovarian reserve testing, and long-term fertility outcomes are warranted before translation to clinical practice.

Author contribution

Study conception and design: GŞ, SE, ZA; data collection: GŞ, SE; analysis and interpretation of results: GŞ, SE, ZA; draft manuscript preparation: GŞ, SE. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Local Ethics Committee (Protocol no. 52338575-121/October 18, 2016).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Presentation and clinical outcome of adolescents with Graves' disease

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ABSTRACT

Background: Only a limited number of studies have investigated the characteristics of pediatric Graves' disease (GD). These studies include limited number of participants with varying treatment protocols, definition of remission, and follow-up duration.

Objective: This study aimed to determine the clinical characteristics, remission and relapse rates of adolescents with GD, focusing on potential predictors of remission at diagnosis in adolescents receiving antithyroid drugs (ATD).

Methods: Clinical, laboratory, and radiologic features of 19 patients (F/M:13/6) under 18 years of age, who were followed for GD from 2013 to 2025 at our hospital were retrospectively assessed. Remission was defined as sustained euthyroid state without relapse for at least 12 months after discontinuing ATD.

Results: Patients were diagnosed with GD at a median age of 15 years (IQR: 11.6-15.9). 7 (36.8%) presented with palpitation while 3 (15.8%) presented with weight loss. Tachycardia was observed in 9 (47.4%) and hypertension in 1 (5.3%). Goiter was detected in 13 (68.4%) and ophthalmopathy in 8 (42.1%). Thyroid ultrasonography revealed goiter (6.6 SDS, IQR: 3.6-10.3). 18 (94.7%) of patients had findings consistent with thyroiditis and 4 (21.1%) had thyroid nodules.

Five patients were solely treated with methimazole (MMI) while 14 received both MMI and a β-blocker. Median initial MMI dose was 0.3 mg/kg/day (0.2–0.4). Median follow-up time was 13.0 months (4.5–96.0). MMI was discontinued after a median of 38 months (20–96) at a median dose of 0.02 mg/kg/day (range, 0.02–0.03) in 8 (42.1%) of patients. GD (or thyrotoxicosis) was relapsed in 5 (62.5%) of pateints after a median of 4 months (3–22). Remission was achieved in 3 (15.7%). It was observed that patients with higher thyroid volume SDS at diagnosis tended to have a higher relapse rate. Definitive treatment methods, including radioiodine ablation (n=2) and total thyroidectomy (n=3), were performed in 26.3%, and papillary thyroid carcinoma was detected in one.

Conclusion: ATD is an effective treatment option in adolescents with GD. Thyroid volume at diagnosis may serve as a potential predictor of remission hence further studies are needed to confirm this observation. It should also be noted that thyroid nodules in children with GD may be associated with papillary thyroid carcinoma and therefore thyroid nodules warrant careful evaluation.

Keywords: Graves' disease, adolescence, thyroid nodule, hyperthyroidism, methimazole

INTRODUCTION

Graves' disease (GD) is an autoimmune disorder in which thyroid-stimulating hormone (TSH) receptor antibodies (TRAb) stimulate thyroid gland, leading to excessive secretion of thyroid hormones. It is the most common cause of hyperthyroidism in childhood [1]. Typical clinical manifestations include findings of hyperthyroidism such as tachycardia, hypertension, tremor, weight loss despite increased appetite, nervousness, hyperactivity, menstrual irregularities, heat intolerance, and diarrhea, in addition to findings of goiter and ophthalmopathy on physical examination [2]. GD is rarer in children than adults and tends to present with more severe symptoms at onset. Its incidence is approximately 0.1 per 100,000 person-years in children and 3 per 100,000 person-years in adolescents [3].

Main treatment strategies for GD include long-term pharmacological treatment with antithyroid drugs (ATD), radioactive iodine ablation (RAI), and total thyroidectomy. European Thyroid Association (ETA) guidelines recommend long-term pharmacologic approach as the first-line treatment for children with GD. Although RAI and total thyroidectomy are accepted as definitive second-line treatment options, the choice among these approaches should be determined based on patient-specific factors (such as thyroid volume and disease severity), as well as local practices and available resources by clinicians [4]. Efficacy and adverse effect profiles of these treatment options vary between pediatric and adult populations.

Propylthiouracil (PTU), methimazole (MMI), and carbimazole (CBZ) are ATDs used in GD. MMI which inhibits iodothyronine organification and reduces thyroid hormone synthesis is the first choice in children [5,6]. PTU, is no longer used because of its frequent and serious adverse effects, particularly severe hepatotoxicity [7]. In patients with moderate to severe symptoms of hyperthyroidism, a cardioselective beta-blocker (i.e. atenolol or propranolol) may be administered along with ATDs to alleviate symptoms until euthyroid state is achieved [6]. Adverse reactions are more frequent in pediatric population. Minor and usually transient side effects (i.e. rash, arthralgia, myalgia, and mild elevation of liver enzymes) have been reported in 20-35% of subjects treated with MMI [8,9]. Severe adverse effects such as agranulocytosis, Stevens-Johnson syndrome, and hepatic dysfunction have been observed in about 0.5% [9].

Remission with ATD can be achieved in 30-70% of adults [5]. It is much lower in pediatric population [4]. Relapse risk of children with GD is also lower than that of adults; approximately 20–30% of pediatric cases experience relapse after two years of continuous ATD [2,10]. A limited number of studies including small number of participants have investigated characteristics of children with GD. Treatment protocols, definitions of remission, and follow-up duration vary among centers, and many patients are lost to follow-up on the long term. Therefore, this study aimed to determine clinical characteristics, remission and relapse rates of adolescents with GD, focusing on identifying potential predictors of remission at diagnosis in those receiving ATD.

METHOD

46 patients (F/M: 37/8) under the age of 18 who were followed at our center for hyperthyroidism from 2013 to 2025 were retrospectively evaluated. Of these, 19 were tested positive for TRAb and were diagnosed with GD (Figure 1). Twenty-seven were tested negative for TRAb and were tested positive only for thyroid autoantibodies (anti-thyroid peroxidase (anti-TPO) and/or anti-thyroglobulin (anti-Tg)) and were diagnosed with hyperthyroidism due to Hashimoto thyroiditis and were excluded from the study group.

Demographic characteristics (age, sex), medical and family history, anthropometric measurements (bodyweight, height, and body mass index [BMI]), and findings of physical examination of patients diagnosed with GD were recorded retrospectively from medical records. BMI was calculated using bodyweight (kg)/height (m^2) formula. Height, bodyweight, and BMI standard deviation scores (SDS) were calculated according to age and sex-specific reference data from the Centers for Disease Control and Prevention (CDC) charts.

Laboratory parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), TSH, free T4 (fT4), free T3 (fT3), TRAb, anti-TPO, and anti-Tg, were retrospectively extracted

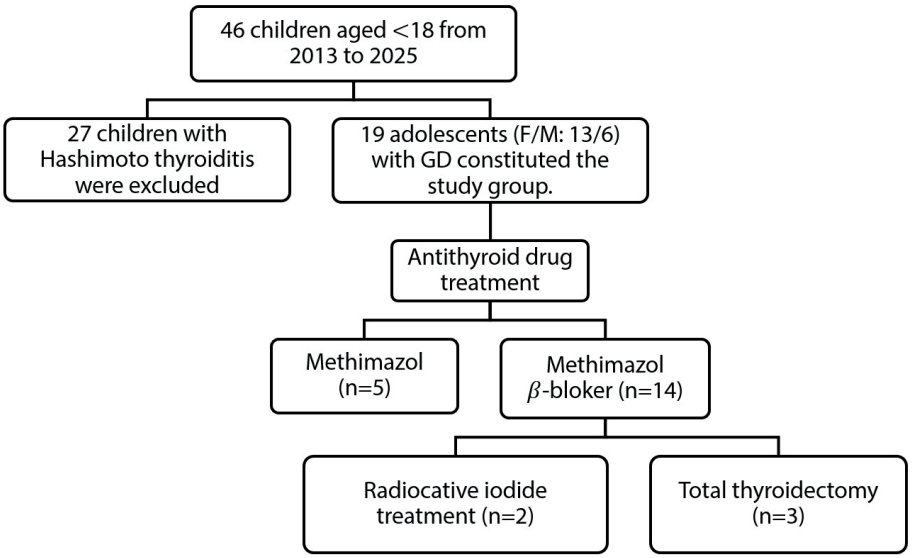

Figure 1. Clinical and treatment characteristics of the study group

from medical records. Serum levels of TSH, fT4, fT3, and thyroid autoantibodies were measured by chemiluminescence assay (Abbott Architect 12000). Reference ranges were 3.3–4.8 ng/dL for fT3, 0.7–1.5 ng/dL for fT4, and 0.4–4.5 IU/mL for TSH. Tachycardia was defined as heart rate exceeding age and sex specific references. On physical examination. Hypertension was defined as systolic and/or diastolic blood pressure above the 95th percentile of age, gender and height specific norms. Thyroid ultrasonography (USG) was performed at diagnosis and when clinically indicated by an experienced radiologist. Findings, including thyroid gland volume and parenchymal characteristics, were recorded. Thyroid gland volume was compared with age and sex specific references, and SDS were recorded. Ophtalmologic examination was conducted by an ophtalmologist in all of the patients with GD.

Anthropometric measurements and laboratory parameters were repeated every three months and when clinically indicated. Remission was defined as maintenance of euthyroid state and absence of relapse for at least 12 months after discontinuation of ATD [1,11]. Patients with GD were categorized into two groups: those who achieved remission (n=3) and those who relapsed (n=5) and clinical, laboratory, and radiological characteristics at diagnosis were evaluated.

Ethical approval

This study was conducted according to Decleration of Helsinki and local ethical approval for this study was obtained (Date: 08/05/2024; number: 2024-BÇEK/75).

Statistical analysis

Analysis was conducted in SPSS version 22.0 for Windows software package (IBM Corp. Armonk, NY). The Shapiro–Wilk test was used to assess the normality of data distribution. Descriptive statistics and categoric variables were presented as frequency (n) and percentage (%), numeric variables were presented as mean, standard deviation, median, interquartile range.

RESULTS

19 patients (F/M: 13/6) with GD were included. 7 (36.8%) patients presented with palpitations while 3 (15.8%) patients had weight loss, 3 (15.8%) patients had ocular symptoms, and 3 (15.8%) patients had a family history of thyroid disease. Neck swelling suggestive of goiter was noticed in one, and in another, decreased school performance was the presenting complaint (Table 1). Family history of thyroid disease was present in 14 (73.7%) patients. On physical examination, 9 (47.4%) patients were tachycardic and 3 (5.3%) patients were hypertensive. Median weight was -0.4 SDS (IQR: -1.7/1.5), median height was 0.1 SDS (IQR: -0.4/0.5), and median BMI was -1.4 SDS (IQR: -1.8/0.3). Goiter was observed in 13 (68.4%) patients and ophthalmopathy in 8 (42.1%) patients and all of them were pubertal (Table 1).

Table 1. Descriptive findings, presenting complaints and findings oo phsical examination in children with GD

	Results
Sex (F/M)	13/6
Median age (years)	15 (IQR: 11.6-15.9)
Family history of thyroid disease, n (%)	14 (73.7%)
Presenting complaints	
Palpitations, n (%)	7 (36.8%)
Weight loss, n (%)	3 (15.8%)
Ocular symptoms, n (%)	3 (15.8%)
Family history of thyroid disease, n (%)	3 (15.8%)
Neck swelling, n (%)	1 (5.2%)
Decreased school performance, n (%)	1 (5.2%)
Physical examination	
Median weight, SDS (IQR)	-0.4 (-1.7/1.5)
Median height, SDS (IQR)	0.1 (-0.4/0.5)
Median BMI, SDS (IQR)	-1.4 (-1.8/0.3)
Tachycardia, n (%)	9 (47.4%)
Hypertension, n (%)	3 (5.3%)
Goiter, n (%)	13 (68.4%)
Ophthalmopathy, n (%)	8 (42.1%)

At a median age of 15 years (IQR: 11.6-15.9), they were diagnosed with GD as median TSH was 0.008 mIU/mL (IQR: 0.08–0.008), fT4 was 2.6 ng/L (IQR: 1.5-3.4), and fT3 was 12.4 ng/L (IQR: 6.5-20.0). Liver transaminases at diagnosis were elevated in 15.3%. All of the patients were TRAb positive, and 89.5% were positive for anti-TPO and/or anti-Tg. Thyroid USG of the study group revealed goiter (thyroid gland volume: 6.6 SDS, IQR: 3.6-10.3). Findings consistent with thyroiditis were observed in 18 (94.7%) patients, and thyroid nodule were detected in 4 (21.1%) patients .

Five patients were treated with MMI alone while 14 patients received both MMI and a β-blocker. Median initial MMI dose was 0.3 mg/kg/day (0.2-0.4). Median follow-up time was 13.0 months (4.5-96.0). MMI was discontinued and remission was evaluated in 8 (42.1%) patients after a median of 38 months (20-96) at a median MMI dose of 0.02 mg/kg/day (0.02-0.03). However, relapse occurred in 5 (62.5%) patients after a median of 4 months (3-22). Remission was achieved in three (15.7%) patients. Due to the limited number of patients achieving remission, potential predictors of remission could not be statistically analyzed; however, patients with higher thyroid volume SDS at diagnosis tended to have a higher relapse rate. Adverse effects related to medication were not observed during follow-up.

Definitive treatment strategies including RAI (n=2) and total thyroidectomy (n=3) were applied in 26.3%.. All of these patients had initially received ATD. RAI was indicated in one patient who presented with marked goiter (grade III) and exophthalmos and did not achieve remission after three years of ATD. In another, RAI was chosen as she relapsed four months after discontinuation of ATD following four years of treatment. Among those who underwent total thyroidectomy, one had been using MMI for nine years, with three unsuccessful discontinuation attempts. In another one, a 14×10×10mm heterogeneous nodule with focal calcification was detected on thyroid USG four months after initiating MMI. Fine-needle aspiration biopsy revealed papillary thyroid carcinoma. She underwent total thyroidectomy with lymph node dissection and has since been followed with suppressed TSH levels under Na-levothyroxine. The remaining patient had experienced relapse after discontinuation of ATD following three years of treatment, and total thyroidectomy was performed as thyroid nodule was detected.

DISCUSSION

This study presents 19 adolescents diagnosed with GD from a single center. Consistent with the literature, the majority were female, and most of them had a family history of GD [12]. They presented with symptoms of hyperthyroidism, were diagnosed based on laboratory findings, and received ATD as first-line treatment. Median follow-up time was 13 months, and at a median of 38 months, ATD was discontinued for evaluation of remission. Remission was achieved in 15.7%. Although being at the lower end of the reported range (11–49%), this rate was comparable to those reported in other pediatric GD studies [1,2,13]. These findings supported the view that remission rates in pediatric GD are considerably lower than those reported in adults (39.5%-85%) [1].

Studies evaluating optimal timing for treatment discontinuation of ATDs report variable results. Current guidelines recommend tapering or discontinuing ATD after at least two years of maintained euthyroid state. However, these recommendations are largely based on adult studies. More recent studies in children and adolescents have shown that those using ATD

who remain euthyroid for prolonged periods may sustain remission for up to four years [1]. In 2012, Léger et al. reported that among 154 French children with GD, remission was achieved in 20%, 37%, 45%, and 49% of patients after 4, 6, 8, and 10 years of ATD, respectively [3]. Wong et al. compared patients who achieved remission with those who did not and reported that the duration of ATD treatment was significantly longer in the remission group (28 vs. 21 months; p=0.024) [1]. In another study, patients who received long-term MMI (96-120 months) were compared with those treated for a shorter period (median=22 months), and those who received long-term treatment had threefold higher remission rate [14]. These findings suggest that relatively lower remission rates observed in this study when compared with previous studies may be attributed to the relatively shorter follow-up duration [1,2,13].

Thionamides inhibit TPO enzyme blocking the oxidation and organification of iodine. The precise mechanism by which thionamides reduce TRAb and induce remission in patients with GD remains to be elucidated. Several mechanisms have been proposed. Studies have shown that hyperthyroidism itself increase TRAb production, leading to persistence and even exacerbation of autoimmunity. It was shown that by controlling thyroid autoimmunity, this vicious cycle was interrupted in patients with GD who remain euthyroid for extended periods. As a result, the likelihood of remission increased while recurrence was prevented [1]. Changes in antigen presentation or a direct immunomodulatory action of ATDs were put forward as possible mechanisms [1]. These proposed mechanisms and observations suggest that longer utilization of ATD prior to proceeding with definitive treatment options may be more appropriate for childhood GD. In line with this, the latest ETA guideline recommends maintaining ATDs for at least three years, or up to five years in patients with a lower likelihood of remission [10].

One of the objectives of this study was to determine prognostic factors for remission at diagnosis and to define clinical characteristics that may justify earlier consideration of definitive treatment in pediatric GD. However, due to limited number of patients who achieved remission, statistical analysis of these potential predictors could not be performed. It was observed that relapse rate was higher in patients with higher thyroid volume SDS at diagnosis. Our observation was consistent with previous studies. Previous studies evaluating predictive clinical features for remission or relapse concluded that younger age at diagnosis, male sex, non-Caucasian ethnicity, higher TRAb and fT4 at diagnosis, larger thyroid gland volume, and absence of other autoimmune disorders were associated with lower remission and higher relapse rates [2,3,13-16]. In another study, time required for TRAb normalization was proposed to be the strongest predictor of remission. It was reported that patients whose TRAb levels normalize within the first year have a 70% likelihood of remission, whereas if TRAb levels normalized during the second year they had 50% likelihood [2].

Remission rates with ATDs are lower in childhood. As life expectancy is longer and there are potential adverse effects of definitive treatment options, ATDs are usually the preferred first-line treatment. In this study, 26.3% of adolescents with GD who have received long-term ATD (3–9 years) but could not discontinue treatment or those with suspected malignancy had to proceed with definitive treatments of either RAI or total thyroidectomy. RAI exerts its effect by inducing thyroiditis through β-emission radiation, leading to follicular cell destruction and subsequent hypothyroidism. RAI is recommended in those who fail to achieve remission, demonstrate relapse, adverse drug reaction or poor adherence to ATD [12]. Total thyroidectomy may be considered in patients with larger thyroid gland who fail to achieve remission with ATD with severe orbitopathy. Other reasons may be the need for rapid control of hyperthyroidism, or patient preferences [12].

Thyroid USG revealed nodules in 21.1% of the patients included in the study, and fine-needle aspiration biopsy identified papillary thyroid carcinoma in one, for which total thyroidectomy was performed. Papillary thyroid carcinoma has previously been reported in children with GD. In a study by McFarland et al., 1.8% of 151 children with GD had papillary thyroid carcinoma [17]. In a meta-analysis evaluating the prevalence of papillary thyroid carcinoma among adults with GD, papillary thyroid carcinoma was detected in 22.2% with solitary thyroid nodule [18]. Tuli et al. reported a 16-year-old patient with hereditary spherocytosis and GD who underwent total thyroidectomy after

euthyroid state could not be achieved following one year of ATD. Incidentally, a 2.8-mm papillary thyroid carcinoma foci was identified in the thyroidectomy specimen [19]. Shimura et al. reported an 8-year-old with GD in whom thyroid nodule was not detected at diagnosis. Four years later, the patient developed rapidly progressive metastatic papillary thyroid carcinoma. The authors suggested that this aggressive course might be associated with low expression of *SLC5A5* in the tumor tissue, preservation of TRAb expression, and the presence of a *TFG/NTRK1* rearrangement [20]. Despite this observation of Shimura et al. of a more aggressive course, Macfarland et al. noted that when children with GD and papillary thyroid carcinoma and those with papillary thyroid carcinoma were compared, significant difference in tumor burden, extrathyroidal extension, lymph node metastasis, or prognosis were not found. They reported that incidental papillary thyroid microcarcinomas were more frequent among patients with GD [17].

Limitations

This study has several limitations. Firstly, this study was carried out in a limited number of patients with relatively short follow-up duration. Due to limited number of patients who achieved remission, statistical analysis of these potential predictors could not be performed. Secondly, due to the retrospective design, some of the important data were lost.

CONCLUSION

This single-center study highlights the clinical characteristics of adolescents with GD. ATD is proven to be an effective treatment in adolescents with GD. Although not statistically significant, larger thyroid volume at diagnosis may serve as a potential marker for predicting lower likelihood of remission hence further studies are needed to confirm this observation. Thyroid nodules in children with GD should also be carefully evaluated, as they may be associated with papillary thyroid carcinoma. Given the rarity of pediatric GD, multicenter studies with larger cohorts are warranted to identify predictive factors of remission and to better guide treatment strategies in this population.

Author contribution

Study conception and design: YU and ADB; data collection: NY; analysis and interpretation of results: YU, NY and ADB; draft manuscript preparation: YU, NY. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ankara Atatürk Sanatoryum Training and Research Hospital ethics committee (Protocol no. 2024-BÇEK/75/08.05.2024).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Predictors of myeloproliferative neoplasm in non-cirrhotic portal vein thrombosis: a comparative analysis with hereditary thrombophilia-related cases

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ABSTRACT

Objective: Non-cirrhotic portal vein thrombosis (PVT) is rare in patients without cirrhosis or intra-abdominal malignancy, commonly associated with thrombophilia or myeloproliferative neoplasms (MPNs). Comparative studies on clinical and laboratory features of MPN- versus thrombophilia-related PVT are limited. This study aimed to examine etiological differences and identify parameters that may aid differential diagnosis.

Materials and Methods: In this retrospective cross-sectional study, 73 adult patients with non-cirrhotic PVT due to MPNs or hereditary thrombophilia were included. Clinical, laboratory, imaging, and endoscopic data were collected from records. Continuous variables were analyzed using t-test or Mann-Whitney U test, and categorical variables using chi-square or Fisher's exact test. Multivariable logistic regression and ROC analysis identified predictors of MPN-associated PVT.

Results: Platelet counts were significantly higher in the MPN group than in the thrombophilia group ($p<0.001$). Hepatomegaly and portal double ductopathy (PDD) were more frequent in MPN, with the difference for PDD being significant ($p=0.032$). Splenic/superior mesenteric vein involvement occurred in 41.7% versus 26.5%, and portal vein cavernous transformation (PVCT) in 79.2% versus 57.1%; these differences were not statistically significant. In multivariable analysis, platelet count was the only independent predictor of MPN ($p=0.003$). ROC analysis showed an AUC of 0.79, with a cutoff $\geq 161\times10^3/\mu L$ yielding 85% sensitivity and 61% specificity.

Conclusion: Platelet count is a strong, independent marker for distinguishing MPN-related non-cirrhotic PVT. Although PDD and PVCT are more frequent in MPN, platelet level offers a rapid, practical parameter for differential diagnosis. These findings provide valuable guidance for clinical practice and patient selection for advanced genetic testing.

Keywords: non-cirrhotic portal vein thrombosis, myeloproliferative neoplasms, hereditary thrombophilia, platelet count, portal vein cavernous transformation

INTRODUCTION

Non-cirrhotic PVT is a rare clinical condition characterized by thrombosis of the portal vein, and sometimes the mesenteric veins, in the absence of cirrhosis or intra-abdominal malignancy [1]. In the general population, the lifetime risk of PVT from all causes is approximately 1% [2]. Although PVT is common in patients with cirrhosis (5-24%; 6-64% in autopsy studies), its prevalence in individuals without chronic liver disease is not well established [3].

The major recognized risk factors for the disease include inherited or acquired prothrombotic conditions, hepatobiliary malignancies, intra-abdominal infections or inflammatory processes, and MPNs [3]. According to previous studies, an underlying etiology can be identified in nearly 70% of non-cirrhotic PVT cases [4]. In our previous study, an underlying etiology was identified in 78.8% of cases [5]. In European series, the most common risk factors are thrombophilia (42-50%) and MPNs, with the JAK2 V617F mutation particularly prevalent among the latter [4]. Thrombophilic conditions that can lead to PVT include paroxysmal nocturnal hemoglobinuria, antiphospholipid syndrome, hyperhomocysteinemia, deficiencies of protein C, protein S, or antithrombin III, mutations in Factor V Leiden or Factor II, methylenetetrahydrofolate reductase (MTHFR) gene mutation, among other causes [6]. MPNs are identified as the underlying cause in approximately 20-30% of patients with non-cirrhotic, non-malignant PVT [7]. Consistent with this, in our internal medicine specialization thesis, this proportion was found to be 20.2% [5].

The diagnostic approach to non-cirrhotic PVT is based on thrombophilia assessment and appropriate imaging studies. The American Association for the Study of Liver Diseases (AASLD) and the Baveno VII consensus recommend testing for inherited and acquired thrombophilias, while low-risk genetic tests are not routinely advised. The exclusion of cirrhosis is a crucial step in the diagnostic process and may be supported by contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), liver stiffness assessment, and, when indicated, liver biopsy. Ultrasound, CT, and MRI are the main modalities for diagnosing PVT, with contrast-enhanced studies providing information on thrombus extent, complications, and differentiation from neoplastic thrombi [8]. Diagnosis of MPN in non-cirrhotic PVT can be challenging, as peripheral blood counts may be normal or low in the presence of portal hypertension and hypersplenism. Therefore, testing for the JAK2 V617F mutation, found in ~95% of patients with polycythemia vera (PV) and ~50% of those with essential thrombocythemia (ET), is recommended. Additionally, CALR mutation analysis should be considered in cases with platelet counts $>200\times10^3/\mu L$ and spleen size ≥16 cm, and bone marrow biopsy may be warranted if necessary [1].

Although most studies have examined the association between MPN and PVT, analyses comparing the clinical and laboratory features of MPN-related versus hereditary thrombophilia-related PVT are limited. Moreover, advanced diagnostic tests, including genetic testing, JAK2 mutation analysis, and bone marrow examination, are available only at select centers, and the time required to obtain results means that the availability of rapid and reliable differentiating parameters remains uncertain. The differential diagnosis between MPN-related and thrombophilia-related PVT is important for short-term management, including treatment strategies and thrombotic complication control, and provides guidance for long-term considerations such as disease prognosis, follow-up planning, genetic counseling, and lifelong thrombotic risk management. This highlights the need for further research to identify rapid and reliable differentiating parameters. The aim of this study was to compare the clinical and laboratory features of MPN- and thrombophilia-related etiologies in patients with non-cirrhotic PVT and to identify parameters that may aid in differential diagnosis.

MATERIALS AND METHODS

Study Design: This retrospective, analytical cross-sectional study included 74 patients with non-cirrhotic PVT, whose etiology was attributed to MPN or inherited thrombophilia, selected from 119 patients in the archives of Hacettepe University Faculty of Medicine between 1970 and 2011. The study reporting followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist.

Patient Population: Patients were classified into two etiological groups: MPN (n=25) and those with at least one inherited thrombophilia (n=50). One patient with concomitant MPN and inherited thrombophilia was excluded. The MPN group included 24 patients and the thrombophilia group 49 patients.

Data Collection Process: Demographic data, presenting symptoms, physical examination findings, laboratory results, abdominal ultrasonography (US), endoscopic evaluations, and endoscopic retrograde cholangiopancreatography (ERCP) findings were retrospectively collected from patient records.

Variables and Definitions: The independent variables included both continuous and categorical parameters. Continuous variables included age, age at diagnosis, liver enzyme tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP)], total bilirubin, albumin, international normalized ratio (INR), hemoglobin, and platelet count. Since platelet levels may be influenced in patients who underwent splenectomy, their values were excluded from analysis.

Categorical variables included demographic and clinical variables [sex; abdominal pain, distension, fatigue, melena, hematemesis, hematochesia, nausea, vomiting; physical examination: pallor, splenomegaly, hepatomegaly, jaundice, venous abdominal collaterals, ascites, splenectomy scar], imaging and interventional findings [splenic and superior mesenteric vein involvement, PVCT, mild chronic hepatic changes (ultrasound-assessed)], endoscopic and ERCP findings [PDD, sclerosing cholangitis (SC), normal or abnormal endoscopic findings], comorbid conditions (diabetes, cardiovascular diseases, thyroid disorders, rheumatologic diseases, additional hematologic abnormalities), and other clinical conditions (cholelithiasis).

The dependent variable was the etiology of non-cirrhotic PVT, into two categories: MPN and thrombophilia.

Ethical Approval: Ethical approval for the internal medicine specialization thesis titled "Etiologic Distribution of Chronic Noncirrhotic Portal Vein Thrombosis in Adult Patients" (completed August 1, 2011; YÖKSİS Thesis No: 282140) was obtained from the Ethics Committee of Hacettepe University Faculty of Medicine before the study commenced. This study used only archival data from the thesis, involved no new interventions, addressed entirely new research questions, and no duplicate publication (salami slicing) occurred.

Statistical Analysis: All analyses were performed using IBM SPSS Statistics version 27. The distribution of continuous variables was assessed by the Shapiro-Wilk test. Means and 95% confidence intervals (CI) were calculated. Comparisons between groups were conducted using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

For categorical variables, frequencies and percentages were calculated, and differences were analyzed using the Pearson chi-square test or Fisher's exact test (2-sided) when the expected cell frequency was less than 5. To identify predictors of PVT etiology, multivariate logistic regression (MLR) analysis was performed. Platelet count, PVCT, and hepatomegaly were included in the model. Results were reported as B coefficients, standard errors (S.E.), Wald statistics, odds ratios (OR), and 95% CI.

The overall model significance was assessed using the Omnibus Tests of Model Coefficients, and model fit was evaluated with the Hosmer-Lemeshow test. Statistical significance was set at $p < 0.05$.

Power Analysis: Due to the retrospective design and the use of a fixed archival dataset, no prior power analysis was performed; all eligible cases were included in the study. The precision of the findings was assessed using 95% CI.

RESULTS

The mean age in the MPN group was 44.5 years, while it was 46.9 years in the thrombophilia group; no statistically significant difference was observed between the groups (p=0.630). The mean age at diagnosis was 38.6 years (95% CI: 33.7-43.4) in the MPN group and 37.1 years (95% CI: 32.2-42.0) in the thrombophilia group, with no significant difference between the groups (p=0.526) (Table 1).

Table 1. Continuous variables of patients with myeloproliferative neoplasm– and thrombophilia-related portal vein thrombosis

Variables	Etiology of PVT	n	Mean [95% CI]	p-value
Age (years)	MPN	24	44.5 (38.8-50.3)	0.630
	Thrombophilia	49	46.9 (42.5-51.2)	
Age at diagnosis (years)	MPN	24	38.6 (33.7-43.4)	0.526
	Thrombophilia	49	37.1 (32.2-42.0)	
INR	MPN	24	1.30 (1.24-1.35)	0.262
	Thrombophilia	49	1.30 (1.23-1.36)	
ALT (U/L)	MPN	24	34.1 (23.8-44.5)	0.599
	Thrombophilia	48	33.6 (25.1-42.1)	
AST (U/L)	MPN	24	37.6 (29.0-46.3)	0.473
	Thrombophilia	48	38.0 (29.7-46.4)	
GGT (U/L)	MPN	23	95.0 (48.4-141.6)	0.125
	Thrombophilia	48	57.6 (33.5-81.8)	
ALP (U/L)	MPN	23	183.0 (139.0-226.9)	0.672
	Thrombophilia	48	205.7 (149.8-261.7)	
Total bilirubin (mg/dL)	MPN	23	1.25 (0.82-1.67)	0.606
	Thrombophilia	48	1.60 (1.16-2.03)	
Albumin (g/L)	MPN	23	3.9 (3.6-4.1)	0.900
	Thrombophilia	47	3.9 (3.7-4.0)	
Hemoglobin (g/dL)	MPN	24	12.7 (11.3-14.1)	0.171
	Thrombophilia	49	11.7 (11.0-12.5)	
*Platelet (10^3/μL)	MPN	20	430 (273-587)	<0.001
	Thrombophilia	41	172 (126-218)	

PVT: Portal Vein Thrombosis

n: Number of patients

CI: Confidence Interval

MPN: Myeloproliferative Neoplasm

*Platelet counts of patients with prior splenectomy were excluded from the analysis.

INR values were similar between patients with MPN- and thrombophilia-associated PVT (1.30 in both groups; p=0.262). No significant differences were observed in liver function tests; ALT, AST, and total bilirubin levels were comparable between groups. Although not statistically significant, GGT levels were higher in the MPN group [95.0 U/L (48.4-141.6) vs. 57.6 U/L (33.5-81.8); p=0.125], whereas ALP levels were slightly higher in the thrombophilia group [205.7 U/L (149.8-261.7) vs. 183.0 U/L (139.0-226.9); p=0.672]. Platelet counts were significantly higher in the MPN group [430 (95% CI: 273-587) vs. 172 (126-218); p<0.001]. Hemoglobin levels were slightly higher in the MPN group but did not reach statistical significance, while albumin levels were comparable between the two groups (p>0.05) (Table 1).

In the MPN group, 41.7% of patients were female and 58.3% were male, whereas in the thrombophilia group the corresponding proportions were 49.0% and 51.0%. There was no significant difference in sex distribution between the groups (p=0.556). In the MPN group, 79.2% of patients were symptomatic, compared to 85.7% in the thrombophilia group, with no significant difference observed (p=0.478) (Table 2).

Physical examination was present in 95.8% of MPN patients and 87.8% of the thrombophilia group, with no statistically significant difference (p=0.271). Splenomegaly was observed in 83.3% of MPN patients and 75.5% of the thrombophilia group (p=0.448). Hepatomegaly was detected in 29.2% of the MPN group and 12.2% of the thrombophilia group; although not statistically significant, a trend was noted (χ^2=3.152, p=0.076) (Table 2).

Based on ERCP findings, PDD was observed in 55.6% of patients in the MPN group and 14.3% in the thrombophilia group, with a significant difference

Table 2. Distribution of categorical variables in patients with MPN and thrombophilia

Variable	Category	MPN (n)	Thrombophilia (n)	Test statistic	p-value
Gender	Female	10 (41.7%)	24 (49.0%)	$\chi^2 = 0.346$	0.556
	Male	14 (58.3%)	25 (51.0%)		
*Complaint	Present	19 (79.2%)	42 (85.7%)	$\chi^2 = 0.503$	0.478
	Absent	5 (20.8%)	7 (14.3%)		
** Physical findings	Present	23 (95.8%)	43 (87.8%)	$\chi^2 = 1.213$	0.271 (‡0.414)
	Absent	1 (4.2%)	6 (12.2%)		
Splenomegaly	Present	20 (83.3%)	37 (75.5%)	$\chi^2 = 0.576$	0.448 (‡0.555)
	Absent	4 (16.7%)	12 (24.5%)		
Hepatomegaly	Present	7 (%29.2)	6 (12.2%)	$\chi^2 = 3.152$	0.076
	Absent	17 (70.8%)	43 (87.8%)		
PDD (ERCP)	Present	5 (55.6%)	3 (14.3%)	$\chi^2 = 5.487$	0.019 (‡0.032)
	Absent	4 (44.4%)	18 (85.7%)		
SC (ERCP)	Present	3 (33.3%)	12 (57.1%)	$\chi^2 = 1.429$	0.232 (‡0.427)
	Absent	6 (66.7%)	9 (42.9%)		
Splenic vein involvement	Present	10 (41.7%)	13 (26.5%)	$\chi^2 = 1.710$	0.191
	Absent	14 (58.3%)	36 (73.5%)		
SMV involvement	Present	10 (41.7%)	13 (26.5%)	$\chi^2 = 1.710$	0.191
	Absent	14 (58.3%)	36 (73.5%)		
ˣMild chronic hepatic changes	Present	9 (37.5%)	25 (52.1%)	$\chi^2 = 1.365$	0.243
	Absent	15 (62.5%)	23 (47.9%)		
ˣˣEndoscopic findings	Normal	6 (30.0%)	10 (25.0%)	$\chi^2 = 0.170$	0.680
	Abnormal	14 (70.0%)	30 (75.0%)		
ʰAdditional comorbidities	Present	5 (20.8%)	16 (32.7%)	$\chi^2 = 1.098$	0.295
	Absent	19 (79.2%)	33 (67.3%)		
Cholelithiasis	Present	5 (20.8%)	10 (21.3%)	$\chi^2 = 0.002$	0.965
	Absent	19 (79.2%)	37 (78.7%)		
PVCT	Present	19 (79.2%)	28 (57.1%)	$\chi^2 = 3.408$	0.065
	Absent	5 (20.8%)	21 (42.9%)		

*Abdominal pain, abdominal distension, fatigue/weakness, melena, hematemesis, hematochezia, nausea and vomiting, etc.

**Pallor, splenomegaly, hepatomegaly, jaundice, venous abdominal collateral, ascites, splenectomy scar, etc.

***Hepatic vein, inferior vena cava, femoral vein, jugular vein, popliteal vein, etc.

ˣThe evaluation was conducted using liver ultrasound.

ˣˣEsophageal varices, gastric varices, portal hypertensive gastropathy

ʰDiabetes mellitus, cardiovascular disease, thyroid disorders, rheumatologic diseases, additional hematologic abnormalities, etc.

PDD: Portal double ductopathy

ERCP: Endoscopic retrograde cholangiopancreatography

SC: Sclerosing cholangitis

SMV: Superior mesenteric vein

PVCT: Portal vein cavernous transformation

‡Fisher's Exact (2-sided)

between groups (Fisher's Exact test, p=0.032). SC was detected in 33.3% of the MPN group and 57.1% of the thrombophilia group; this difference was not statistically significant (p=0.232) (Table 2).

In addition to portal vein involvement, splenic vein and superior mesenteric vein (SMV) involvement was observed in 41.7% of the MPN group and 26.5% of the thrombophilia group; the difference was not statistically significant (p=0.191), although a higher frequency in MPN patients was noted (Table 2).

On liver ultrasound evaluation, mild chronic changes were detected in 37.5% of the MPN group and 52.1% of the thrombophilia group; the difference was not statistically significant (p=0.243).

The prevalence of cholelithiasis was approximately 21% in both groups, with no significant difference observed (p=0.965) (Table 2).

Abnormal findings on endoscopic evaluation were observed in 70% of the MPN group and 75% of the thrombophilia group; the difference was not statistically significant (p=0.680). The prevalence of PVCT was 79.2% in the MPN group and 57.1% in the thrombophilia group; the difference approached statistical significance (χ^2=3.408, p=0.065) and was higher in the MPN group (Table 2).

Comorbidities, including diabetes mellitus, cardiovascular, thyroid, rheumatologic, and additional hematologic disorders, were observed in 20.8% of the MPN group and 32.7% of the thrombophilia group; the difference was not statistically significant (p=0.295) (Table 2).

In MLR analysis, the relationships between platelet count, PVCT, hepatomegaly, and the etiology of PVT (MPN vs. thrombophilia) were assessed. Platelet count strongly predicted MPN etiology; higher platelet values were significantly associated with increased likelihood of MPN (OR: 0.99 [95% CI: 0.99-1.00], p=0.003). The presence of PVCT showed a trend toward increased MPN probability (OR: 2.75 [95% CI: 0.59-12.84], p=0.198), whereas hepatomegaly was not a significant predictor (OR: 0.75 [95% CI: 0.12-4.91], p=0.765). The Hosmer-Lemeshow test confirmed good model fit, and the Omnibus Test indicated overall model significance (Table 3).

ROC analysis showed that platelet count predicted MPN-associated PVT with an AUC of 0.79 (95% CI: 0.66-0.91, p<0.001), indicating good discriminative ability for distinguishing MPN etiology. Using the maximum Youden index, the optimal cutoff was PLT ≥161×10^3/μL, yielding 85% sensitivity and 61% specificity (Figure 1).

DISCUSSION

In this study, we compared the clinical and laboratory characteristics of patients with non-cirrhotic PVT associated with MPNs or thrombophilia. Our aim was to identify distinguishing features that could aid in the etiological differentiation of PVT.

No significant difference in current age or age at diagnosis was observed between patients with MPN- and thrombophilia-related PVT. Although literature suggests MPN tends to cause PVT at older ages and thrombophilia in younger patients, the similarity in our cohort implies MPN may also

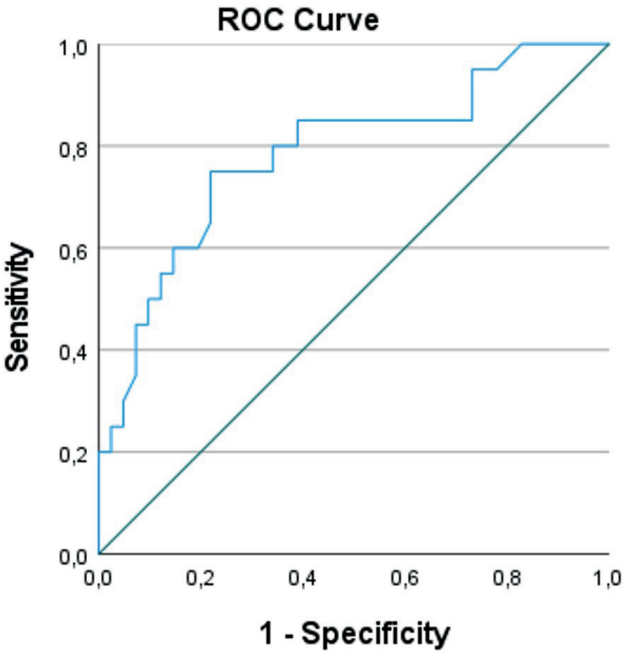

Figure 1. ROC curve for platelet count predicting MPN-associated PVT

Table 3. Multivariate logistic regression analysis for predictors of portal vein thrombosis etiology

Variable	B	S.E.	Wald	OR (95% CI)	p-value
Platelet	-0.006	0.002	8.654	0.99 (0.99-1.00)	0.003
PVCT Reference category: Absent	1.012	0.786	1.657	2.75 (0.59-12.84)	0.198
Hepatomegaly Reference category: Absent	-0.286	0.958	0.089	0.75 (0.12-4.91)	0.765

OR: Odds ratio

CI: Confidence interval

PVCT: Portal vein cavernous transformation

Omnibus Tests of Model Coefficients: χ^2=17.376, df=3, p=0.001

Hosmer-Lemeshow Test: χ^2=12.68, df=8, p=0.123

present earlier. In a study by How et al., 134 patients with MPN were compared to 52 with splanchnic vein thrombosis (SVT)-MPN, showing a significantly lower median age in the SVT-MPN group (47 vs. 56.5 years; p=0.003) [9]. Similarly, Hoekstra et al. reported a median age of 48 years in 44 patients with MPN-related PVT [7]. Overall, these results suggest neither age at diagnosis nor current age distinguishes the two groups.

In the literature, gender distribution in the general PVT population is variable. One study reported 59% of patients with PVT were male and 41% female, with this distribution remaining stable over time [10]. Another study of MPN-associated SVT patients reported a female predominance (65.2%) [11]. In our study, gender distribution was similar in both groups: MPN, 41.7% female and 58.3% male; thrombophilia, 49.0% female and 51.0% male (p=0.556). These findings suggest that gender does not significantly affect PVT etiology or clinical presentation. No studies have directly compared MPN- and thrombophilia-associated PVT regarding gender.

In non-cirrhotic PVT, the most common presenting symptoms are abdominal pain, distension, gastrointestinal bleeding, fever, and ascites. Disease severity depends on etiology and thrombosis extent [12]. In our study, most patients in both groups were symptomatic (MPN 79.2%; thrombophilia 85.7%; p=0.478), and physical examination findings were frequently observed (MPN 95.8%; thrombophilia 87.8%; p=0.271), indicating that non-cirrhotic PVT is generally symptomatic regardless of etiology.

Splenomegaly is common in PVT, typically presenting as left upper quadrant discomfort, pain from splenic infarction, or, occasionally, symptomatic hypersplenism [13]. In our study, splenomegaly was slightly more frequent in the MPN group (MPN 83.3%; thrombophilia 75.5%; p=0.448), but the difference was not statistically significant. These findings indicate that splenomegaly is common in both groups and is not a reliable standalone criterion for etiological differentiation.

Hepatomegaly was more frequent in the MPN group than in the thrombophilia group (29.2% vs. 12.2%; p=0.076), but the difference did not reach statistical significance, likely due to the limited sample size. A previous study reported a hepatomegaly rate of 18% in non-cirrhotic PVT patients with MPN [7]. This may be explained by the increased risk of hepatomegaly in MPN due to portal hypertension and extramedullary hematopoiesis, making the observed trend pathophysiologically plausible. In MLR analysis, hepatomegaly did not significantly predict MPN (OR 0.75, 95% CI 0.12–4.91; p=0.765), indicating it is not a reliable standalone marker for etiological differentiation. Larger prospective studies are needed to clarify hepatomegaly distribution in MPN- and thrombophilia-associated PVT.

In patients with chronic PVT without underlying liver disease, liver function tests are generally normal [14,15]. Marked elevation of cholestatic enzymes may indicate portal cholangiopathy [14]. In our study, ALT and AST levels were similar in both groups, supporting largely preserved liver function in non-cirrhotic PVT. GGT levels were higher in the MPN group, although not statistically significant, which may reflect intrahepatic circulatory disturbances, microthrombosis, or concomitant cholestatic processes. Conversely, higher ALP and total bilirubin levels in the thrombophilia group may result from long-standing PVT affecting the biliary system. Clinically, these findings are relevant for potential complications of portal hypertension. Although not significant, the results suggest a trend toward elevated GGT in MPN and higher ALP and bilirubin in thrombophilia. Larger studies are needed to clarify the clinical relevance of these subtle differences.

Hemoglobin levels were similar between groups, with a mean value of 12.7 g/dL in the MPN group and 11.7 g/dL in the thrombophilia group (p=0.171). This finding indicates that hemoglobin alone has limited value in the etiological differentiation of PVT. Previous studies have reported that hemoglobin levels may appear normal (masked) in patients with MPN-associated (particularly PV) SVT [16]. Our findings are consistent with the characteristic hematological features of MPNs reported in the literature and may contribute to the evaluation of PVT etiology in clinical practice. Larger prospective studies are needed to validate these results.

In our study, platelet counts were markedly elevated in patients with MPN-related PVT, consistent with the characteristic hematological profile of this group. Platelet count also emerged as an independent predictor of etiology, suggesting

its potential utility in differential diagnosis. ROC analysis demonstrated good diagnostic performance in distinguishing MPN-related cases from thrombophilia-associated PVT, with high sensitivity (85%). However, limited specificity indicates that platelet count alone may not suffice as a diagnostic marker and should be interpreted alongside other clinical and laboratory findings. Similarly, ROC analyses in patients with SVT have shown that platelet counts above 190,000/mm^3 are significantly associated with an increased likelihood of JAK2 V617F mutation and MPN. The retrospective, single-center design represents a limitation regarding moderate specificity. Future studies combining hematological parameters with genetic testing are recommended to develop more robust scoring systems for distinguishing MPN-related PVT [17].

Clinical manifestations in patients with PVT include obstructive jaundice, cholangitis, and, in the later stages, choledocholithiasis secondary to pseudosclerosing cholangitis or portal hypertensive biliopathy [13]. Portal cholangiopathy is a complication that may develop in patients with chronic PVT or portal cavernoma. In such cases, porto-portal collaterals can compress the bile ducts, leading to ischemic injury, chronic inflammation, and fibrosis [8]. In our study, PDD was observed more frequently in patients with MPN than in those with thrombophilia, suggesting that it may serve as a potential clinical marker for etiological differentiation. However, the limited number of patients and restricted availability of ERCP in all centers should be considered when interpreting the generalizability of these findings. Portal cavernoma cholangiopathy refers to abnormalities of the bile ducts that develop in patients with chronic non-cirrhotic PVT due to external compression by a portal cavernoma or altered portal blood flow [1]. Supporting this observation, PVCT was more common in patients with MPN compared to those with thrombophilia (79.2% vs. 57.1%). Interestingly, although not statistically significant, sclerosing cholangitis (SC) findings on ERCP were more frequently observed in thrombophilia patients than in MPN patients (57.1% vs. 33.3%), in contrast to PDD. This indicates that SC can also occur in non-cirrhotic PVT etiologies and is not a reliable standalone marker for etiological differentiation. The small sample size may have limited the power to detect significant differences, highlighting the need for studies with larger cohorts. Additionally, the similar rates of choledocholithiasis in both groups suggest that this condition does not differ between MPN- and thrombophilia-associated PVT.

In our study, vessels involved in addition to the portal vein were evaluated separately. Involvement of the splenic vein and SMV was observed in 41.7% of patients in the MPN group and 26.5% in the thrombophilia group (p=0.191). Although these differences were not statistically significant, the higher rates in the MPN group may suggest a tendency for more extensive involvement of the portal system in these patients. In the literature, splenic vein involvement has been reported in approximately 20% and SMV involvement in approximately 14% of MPN-related SVT cases [18]. Comparative data across different etiologies remain limited.

The literature reports chronic parenchymal changes in the liver even in late-stage non-cirrhotic PVT [8]. In our study, mild chronic changes assessed by ultrasonography were more frequent in the thrombophilia group than in the MPN group (52.1% vs. 37.5%), although not statistically significant. This may be explained by the more isolated and clinically silent progression of PVT in the thrombophilia group and by the sensitivity of ultrasonography. Larger studies are needed to clarify these findings.

Abnormal endoscopic findings, including esophageal varices, gastric varices, and portal gastropathy, were common in both groups (MPN 70.0%; thrombophilia 75.0%), likely reflecting portal hypertension secondary to PVT. This indicates that endoscopic manifestations can appear similarly in MPN- and thrombophilia-related PVT. In one study, esophageal and gastric varices were detected in 79% of MPN-related PVT patients at diagnosis [7], comparable to our findings. However, no comparative studies by etiology have been reported.

The presence of PVCT in patients with PVT suggests chronicity of the disease and is typically accompanied by splenomegaly and collateral formation associated with the portal venous system [13]. PVCT is a compensatory mechanism that develops within a few days following vascular occlusion and becomes fully established within 3-5 weeks [19]. In our study, PVCT was observed in 79.2% of patients in the MPN group and

57.1% in the thrombophilia group (p=0.065). The higher prevalence of PVCT in the MPN group is noteworthy, suggesting that MPN may exert a stronger procoagulant effect in the development of PVT, leading to more frequent obstruction-related cavernous transformation. Clinically, PVCT is an important indicator of portal hypertension and its associated complications; therefore, its presence in patients with MPN may warrant closer monitoring and, if necessary, endoscopic or radiologic intervention. Although PVCT was not statistically significant in MLR analysis, it was associated with MPN and showed a tendency to increase the likelihood of MPN. These findings support the notion that PVCT may be a clinically relevant parameter for distinguishing non-cirrhotic PVT due to MPN from that due to thrombophilia.

Strengths and Limitations: This study is among the few directly comparing clinical and laboratory differences between MPN and hereditary thrombophilia in non-cirrhotic PVT. MLR and ROC analysis demonstrated the high discriminative ability of platelet count in predicting MPN and identified a clinically applicable cut-off, providing a practical parameter for differentiating PVT due to MPN from thrombophilia and guiding further genetic evaluation and treatment planning.

However, the study is retrospective and single-center, carrying a risk of selection bias. The limited sample size, especially in the MPN group, may have prevented some variables from reaching statistical significance. Findings are generalizable only to similar centers and populations; confirmatory studies with larger cohorts in different regions are warranted.

CONCLUSION

Non-cirrhotic PVT in patients with MPN and thrombophilia shows largely similar clinical and laboratory features. However, elevated platelet count emerged as an independent and strong predictor of MPN-associated PVT. Additionally, the higher prevalence of portal cavernous transformation and biliary complications in the MPN group is noteworthy. In patients with thrombocytosis, the possibility of MPN should be considered and supported by other laboratory and genetic tests. Our findings warrant validation in larger prospective studies.

Author contribution

Study conception and design: YSH and YB; data collection: YSH and YB; analysis and interpretation of results: YSH and YB; draft manuscript preparation: YSH and YB. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Ethical approval for the specialty thesis entitled "Etiologic Distribution of Chronic Noncirrhotic Portal Vein Thrombosis in Adult Patients" (completed August 1, 2011; YÖKSİS Thesis No: 282140) was obtained from the Ethics Committee of Hacettepe University Faculty of Medicine prior to its initiation.

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Challenging cervical spondylodiscitis: Is interventional treatment superior to conservative management?

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ABSTRACT

Objective: Cervical spondylodiscitis is a rare spinal infection with limited literature on its management. While antibiotic therapy is critical for infection control, addressing residual pain and functional deficits remains challenging. This retrospective observational study evaluated the efficacy and safety of interventional management in patients with spontaneous cervical spondylodiscitis.

Materials and Methods: Patients were treated with either medical therapy or interventional pain management after completing antibiotic therapy and physical rehabilitation. The outcomes of interventional pain management (Group 1, n=9) and medical therapy (Group 2, n= 12) in improving pain, functional capacity, and quality of life in patients with cervical spondylodiscitis were compared. Treatment responses were assessed using Numerical Rating Scale (NRS), Neck Disability Index (NDI), and SF-12 scores before and after therapy. Changes in cervical lordosis angles were also monitored.

Results: Of the 35 screened patients, 21 met the inclusion criteria, with 12 opting for medical therapy and 9 for interventional treatment. Both groups demonstrated significant improvements in NRS, NDI, and SF-12 scores after treatment ($p<0.05$). Interventional therapy resulted in superior NRS and NDI outcomes compared to medical therapy (NRS: 1.11 vs. 2.33, $p=0.017$; NDI improvement: 76% vs. 56.66%, $p=0.0009$). No significant changes in cervical lordosis angles were observed in either group.

Conclusion: Interventional pain management provides superior pain relief and functional improvement compared to medical therapy alone in patients with cervical spondylodiscitis. Conservative management is effective in appropriately selected cases, offering an alternative to surgery for those without instability or neurological deficits.

Key words: cervical osteomyelitis, interventional pain treatment, cervical spondylodiscitis, spine, pain, infections, injections

INTRODUCTION

Spondylodiscitis is a serious medical condition characterized by infection of the discs in the spine [1,2]. The disease is caused by the invasion of bacteria or fungal agents and can lead to symptoms such as severe pain, fever, instability and neurological deficits. Spondylodiscitis is a highly catastrophic disease and can significantly increase the risk of morbidity and mortality [3,4]. The cervical spine is a rare location for spondylodiscitis due to its relatively better blood and lymphatic supply than other regions of the spine [5].

In the treatment of spondylodiscitis, the primary goal is infection control [6,7]. Therefore, long-term antibiotherapy appropriate to the agent forms the cornerstone of treatment. Afterwards, the aim is to restore pain and functional capacity. This may require medical treatment, physical therapy and interventional pain treatments. Surgery should be preferred only in cases with progressive neurologic deficits and/or severe instability [8].

Since cervical spondylodiscitis is an extremely rare condition, there is a gap in the literature regarding its management. In this study, we aimed to evaluate the efficacy and safety of conservative treatment without indication for surgery by comparing the outcomes of only medical therapy or interventional pain management in patients with spontaneous cervical spondylodiscitis. Our hypothesis suggests that interventional pain management such as trigger point injection, facet joint injection may be an effective method to significantly reduce pain and improve quality of life in patients with cervical spondylodiscitis when medical therapy alone is inadequate.

A preliminary version of this work has been previously made available as a preprint on Research Square (link was anonymized)

MATERIALS AND METHODS

The study was conducted according to EQUATOR STROBE observational study guidelines. After obtaining approval from the Toros University Clinical Research Ethics Committee of local board (123/27.10.23), the files of patients diagnosed with vertebral osteomyelitis between December 2017, and January 2023, were retrospectively screened. The center of this study is a tertiary-care state hospital serving approximately 1.8 million people. There is only one other tertiary-care university hospital in the region.

After excluding thoracic and lumbar spondylodiscitis cases, cervical osteomyelitis cases were included in the study. All the patients were older than 18 years, and none had a history of malignancy. Patients with severe deformities, progressive neurological deficits and/or instability were also excluded due to necessity of surgical treatment. Patients who did not follow up regularly and who had missing/incomplete data were excluded.

Diagnosis: Diagnosis and treatment plans for patients were determined by a multidisciplinary team consisting of infectious disease specialists, radiologists, physical therapists, pain specialists, and neurosurgeons. Following a comprehensive clinical history and physical examination, all patients underwent a series of tests, including complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), QuantiFERON TB test, Brucella-specific agglutination tests, standing cervical X-rays, and contrast-enhanced MRI. Post-treatment response was monitored based on clinical improvement, CRP decline and long-term MRI contrast reduction. Additionally, deformity progression was tracked by monitoring the cervical lordosis angle on standing cervical X-rays.

Participants: Medical files of patients diagnosed with spondylodiscitis were evaluated. Patients with involvement of the lumbar and thoracic spine, progressive neurological deficit and severe instability and underwent surgical intervention and patients with missing data during follow-up were excluded. After antibiotic therapy and physiotherapy, patients preferred medical treatment, or interventional treatment for pain (Figure 1).

Infection treatment: Monthly follow-up of the patients was carried out by infectious disease physician until inflammation was resolved according to a control MRI. Teicoplanin + ciprofloxacin was given for three months in the presence of pyogenic involvement. In brucellosis,

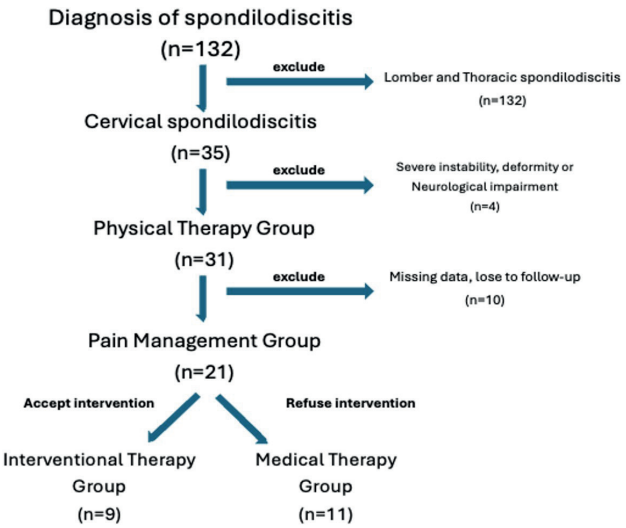

Figure 1. Flow diagram of study ınclusion and exclusion criteria

streptomycin + rifampicin + doxycycline was given for three weeks; then, streptomycin was stopped and the rifampicin + doxycycline treatment was applied for seven months (total treatment time was eight months). In pyogenic cases, if no clinical or radiological response is obtained at the end of the 2-month treatment and the QuantiFERON test is positive, the treatment is switched to isoniazid + rifampicin + ethambutol + pyrazinamide and this regime continued for a minimum of 6 months. The cervical MRI images of all the patients were interpreted by the same radiologist and CRP response was monitored for infectious disease specialist.

Pain and functional treatment: After cure was achieved following antibiotherapy, all patients were first referred to the physiotherapy (PT). After physical therapy, patients with persistent pain were informed about medical pain treatment and interventional pain treatments. Patients were divided into two groups as interventional (group 1) and medical (group 2) according to their preferences.

Interventional Therapy (Group 1): Trigger point injection if there was a tender point in the sternocleidomastoid (SCM) muscle or trapezius, a facet medial branch block if cervical facet tenderness was detected, and a cervical epidural injection was administered if there was accompanying cervical disc herniation. Trigger point injections are performed into the sternocleidomastoid (SCM) muscle and trapezius muscle. Painful tender points are identified through palpation, and 0.1-0.2 ml of lidocaine is injected using an insulin syringe. Additionally, bilateral medial branch blocks of the facet joints are performed at levels including those above and below the affected level due to spondylodiscitis. The procedure is guided by fluoroscopy, and for each facet joint, a combination of 0.5 ml of bupivacaine and dexamethasone is injected (Figure 2). Interlaminar cervical epidural injection was applied through the C7-T1 space, and 8 mg of dexamethasone was administered.

Medical Therapy (Group 2): For patients unwilling to undergo interventional treatment, duloxetine hydrochloride is initiated at a dose of 30 mg/day and increased to 60 mg/day after one month (Figure 1).

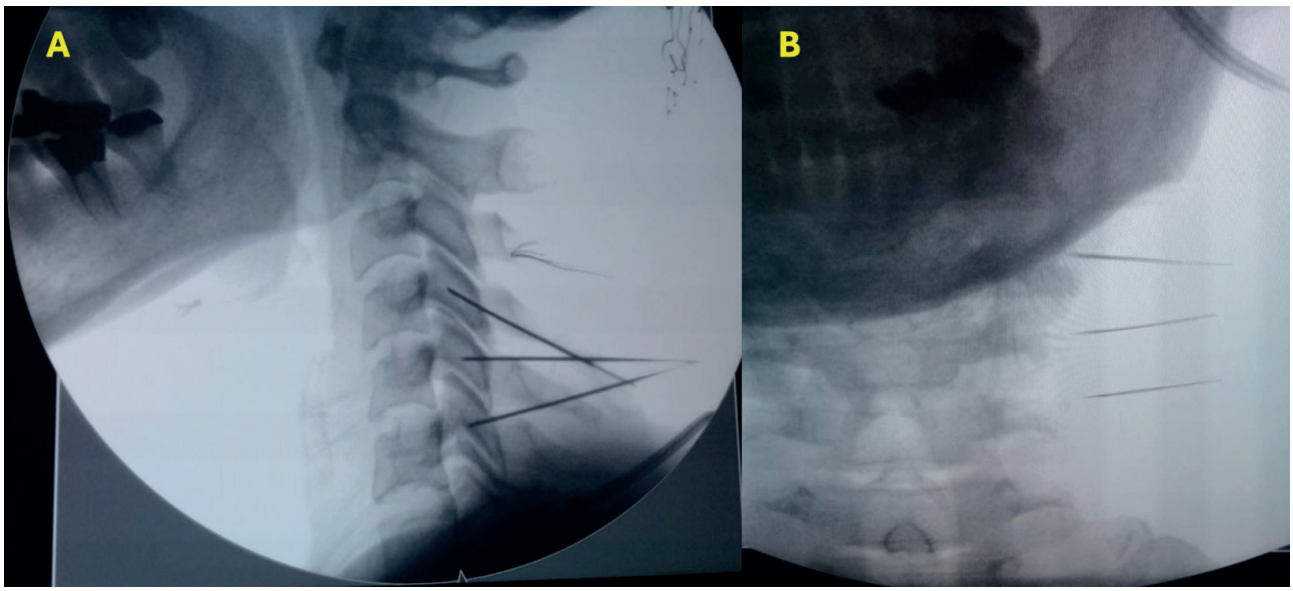

Figure 2. Lateral (A) and antero-posterior (B) Fluoroscopic images of medial branch block of the facet joint

Follow-up: Numerical Rating Scale (NRS) of the patients were recorded before treatment (NRS-0), after antibiotic treatment (NRS-1), after PT (NRS-2), and at six months after medical or interventional treatment (NRS-3). Neck Disability Index (NDI) and SF-12 scores were recorded before and six months after the procedure (Table 1).

Deformity Monitoring: Patients were monitored for the development of kyphosis secondary to spondylodiscitis using standing lateral cervical X-rays. The lordosis angles were measured from the radiographs taken at the time of diagnosis and one year after treatment. The groups were compared in terms of changes in lordosis.

Statistical analysis

IBM SPSS Statistics v. 22 (IBM SPSS, Armonk, New York, United States) software package was used for the statistical analyses of the data obtained from the research. The Shapiro-Wilk test was conducted to check whether the parameters were normally distributed. Descriptive statistical methods (mean, standard deviation, median and interquartile range, and frequency) were used to present the data. Independent quantitative parameters were compared between the groups using the Mann-Whitney U test. Dependent quantitative parameters were compared between the groups using the Wilcoxon test. The comparison of two independent variables that conformed to a normal distribution was made with Student t-test. $P < 0.05$ indicated statistical significance in all the analyses.

RESULTS

A total of 132 patients were diagnosed with spondylodiscitis during the specified period. Of these, 97 were excluded due to involvement of the lumbar and thoracic spine. Four patients were considered unsuitable for study inclusion due to progressive neurological deficit and severe instability and underwent surgical intervention. Ten patients were excluded due to missing data during follow-up. The remaining 21 patients were included in the study. After antibiotic therapy and physiotherapy, 12 patients preferred medical treatment, while 9 patients chose interventional treatment.

Descriptive Data: The average age of the patients was 58.33±10.65 (40-79) years. The average age was 56.22±7.88 (45-69) years in the interventional therapy group and 59.91±12.43 (40-79) years in the medical treatment group (p=0.22). There were 12 (57.14%) female patients and 9 (42.85%) male patients. The mean follow-up period was 28.80±10.15 (14-54) months. Seven patients (33.33%) had involvement at the C6-7 level, six patients (28.57%) had involvement at the C5-6 level, five patients (23.8%) had involvement at the C4-5 level, and three patients (14.28%) had involvement at the C3-4 level. Two patients (9.52%) had clinical and laboratory signs of Brucellosis and took an eight-month antibiotic therapy regimen. The remaining nineteen patients (90.47%) responded well to the wide-spectrum pyogenic antibiotic therapy. None of the patients has received an anti-tuberculosis regimen in this series. None of the patients has a previous surgical history.

Outcome Data: Pre-treatment pain score (NRS1) was 8.90±0.76 (8-10), while post-antibiotic therapy pain score (NRS2) was 5.33±1.46 (3-9), post-physical therapy pain score (NRS3) was 5±1.30 (3-7), and final pain score (NRS4) measured 6 months after medical or interventional pain treatment was 1.80±1.07 (0-4). Pairwise comparisons between groups revealed that NRS1 was significantly higher than NRS2 ($p<0.0001$), there was no significant difference between NRS2 and NRS3 (p=0.5157), and NRS3 was significantly higher than NRS4 ($p<0.0001$) (Table 1).

The mean SF-12 questionnaire score of the patients before treatment was 31.23±2.84 (27-37), while the SF-12 score after medical or interventional pain treatment was 36.61±2.99 (31-42), indicating a significant improvement ($p<0.0001$) (Table 2).

Table 1. Comparison of pain scores between groups with Mann Whitney U test

	Interventional	Medical	P
NRS-1 (Before Treatment)	8.66±0.86	9.08±0.66	0.242
NRS-2 (After Antibiotherapy)	5.44±1.13	5.25±1.71	0.522
NRS-3 (After Physiotherapy)	4.88±1.05	5.08±1.50	0.833

Mean ± Standard Deviation

Table 2. Comparison of SF-12 scores between groups with Mann Whitney U test and change after treatment with Wilcoxon test

	Interventional	Medical	P (Significance between groups)
SF12 Before Treatment	31.44±3.71	31.08±2.15	0.94
SF12 After Treatment	39.77±1.98	37.75±3.38	0.16
SF12 Change	8.33±2.64	6.66±3.44	0.35
P (Significance within time)	**0.0089 ***	**0.0033 ***	

* p< 0.05, Mean ± Standard Deviation

Table 3. Comparison of neck disability index (NDI) percentage between groups with Mann Whitney U test and change after treatment with Wilcoxon test

	Interventional	Medical	P (Significance between groups)
NDI Before Treatment	83.77±8.8	82.5±11.57	0.770
NDI After Treatment	7.77±11.24	25.83±12.77	**0.0049 ***
NDI Change	76±9.21	56.66±11.19	**0.0009 ***
P (Significance within time)	**0.0089 ***	**0.0024 ***	

* p< 0.05, Mean ± Standard Deviation

Table 4. Comparison of cervical lordosis between groups with Mann Whitney U test

	Interventional	Medical	P (Significance between groups)
Cervical Lordosis at Diagnosis	14.97 ± 16.59	10.14 ± 8.39	0.270
Cervical Lordosis after Treatment (one-year)	13.62 ± 8.68	18.58 ± 15.34	0.370

Mean ± Standard Deviation

The pre-treatment Neck Disability Index (NDI) percentage was 41.52±5.12% (33-50), while the post-treatment NDI percentage was 18.09±14.97% (0-52), indicating a significant improvement (p<0.0001) (Table 3).

At the time of diagnosis, the cervical lordosis angles of the patients were found to be 12.21 ± 12.44 (-10.8 - 35.3), while the lordosis angle one year after treatment was determined to be 15.75 ± 11.91 (-8.4 - 38.5). No significant difference was found in the lordosis angles (p=0.26) (Table 4).

Main Results: Medical and interventional pain treatment groups showed no significant differences in NRS1, NRS2, and NRS3 scores obtained before treatment, after antibiotic therapy, and after physical therapy (p values were 0.242, 0.522, and 0.833, respectively). The NRS4 score obtained after the application of different treatments between the two groups was found to be superior in the interventional group (1.11±0.92 (0-2)) compared to the medical treatment group (2.33±0.88 (1-4)) (p=0.017).

Both the medical and interventional pain treatment groups showed significant improvements in SF-12 questionnaire scores before and after treatment (p=0.0089, p=0.0033). However, the magnitude of improvement was not significantly different between the two groups (p=0.35).

Both groups also showed significant improvements in Neck Disability Index (NDI) percentages (p values 0.0089 and 0.0024, respectively). The interventional group demonstrated a greater improvement in NDI (76±9.21% (64-92)) compared to the medical group (56.66±11.19%) (p=0.0009).

No significant difference was observed between the cervical lordosis angles measured at the time of diagnosis and after treatment in both groups.

DISCUSSION

While antibiotic therapy remains the cornerstone of treatment for spondylodiscitis, patients often do not experience adequate improvement in their quality of life, pain scores, and disability following this treatment. Therefore, once the infection is controlled, these patients require additional pain management strategies to facilitate rehabilitation and a return to normal life [9]. This study investigated the effectiveness of interventional or medical treatments following long-term antibiotic therapy for chronic pain, quality of life and disability. The findings suggest that both treatment approaches

had a positive impact on quality of life, disability, and pain scores.

Specifically, facet joint medial branch block and trigger point injections, which target above and below of affected level, were found to be more effective than medical treatment in reducing pain and disability scores. However, no significant difference was observed between the two treatment modalities in terms of quality of life (SF-12 questionnaire). Interventional treatments focus directly on the source of pain, such as facet joints and trigger points [10,11]. This can provide more localized pain relief compared to systemic medication and limit systemic side effects. In a study conducted on patients presenting to the emergency department due to trigger points, one group received trigger point injections while the other group was given NSAIDs. When comparing VAS scores, it was found that the injections were more effective [12]. Because the local anesthetic administered to the trigger point blocks peripheral nociceptive input [13]. Local anti-inflammatory agents may be more effective than systemic treatment, since the main cause of disability and pain in spondylodiscitis is severe inflammation in the affected area [14]. Inflammatory mediators that cause pain are released from degenerated facet joints. Agents administered directly to the area not only exhibit anti-inflammatory effects but also reduce pain by washing away inflammatory cytokines in the area [15]. A critical predictor of the efficacy of systemic therapies is the reaching of a therapeutic concentration of the drug in the blood. This can delay the onset of pain relief, especially in conditions such as spondylodiscitis associated with acute and severe pain. Local applications can provide faster pain relief than systemic therapies by delivering drugs directly to the source of pain. This may be an important advantage, especially in the treatment of acute pain and in improving patient compliance.

This study indicates that the need for surgery in spondylodiscitis is gradually decreasing, and the importance of conservative management is growing. This trend can be explained by advances in antibiotic therapy, improved rehabilitation programs and a better understanding of surgery-related morbidity and mortality. Surgical treatment may be considered a last option in the treatment of spondylodiscitis. In this series, none of the patients who did not require surgical treatment at the time of diagnosis subsequently developed a need for surgery [16-18]. Specifically, it was observed that none of the patients developed kyphotic deformity in the sagittal balance parameter, and thus, there was no need for surgery related to this condition. In the presence of neurologic deficit, progressive deformity or instability, surgery can be necessary. However, surgical treatment also has significant risks. Implant placement may lead to difficulties in infection control and poor bone quality may be associated to implant failure [19-22]. In our series, only 4 (11.42%) of 35 patients with cervical spondylodiscitis required surgical treatment. This finding supports the decreasing role of surgical treatment and the importance of conservative management. Considering the cost-effectiveness of conservative treatment, the most appropriate treatment plan for patients should be determined. However, although the need for surgery is decreasing overall, it is important to realize that surgical intervention is critically important and lifesaving for a specific group of patients. In carefully selected cases, such as those with severe neurological deficits or progressive instability, surgery can provide significant therapeutic benefits and improve quality of life.

Limitations

Due to the rarity of spondylodiscitis in the cervical region, the number of patients included in the study was relatively small. Small samples may limit the power of statistical analyses and the generalizability of findings. Secondly, the study has a retrospective design poses inherent limitations. Third, the choice of treatment was left to the patients, and although information was provided objectively, the hypothesis that interventional treatment was superior may have led to a bias in the treatment decision. Fourthly microbiological diagnosis was not obtained from all patients. In some cases, treatment was initiated before microbiologic diagnosis based on the adequacy of radiological, clinical, and laboratory findings for diagnosis. The heterogeneity of the patient population and the variability in treatment approaches make it difficult to establish standardized therapeutic guidelines.

The findings obtained in the study need to be supported in future studies with randomized and prospective data. In addition, the effect of advanced local methods such as radiofrequency thermocoagulation and cryo-ablation for facet blockage may be examined. Further studies with broader scope and controlled designs are required.

This study suggests that both medical and interventional pain treatments following antibiotic therapy can be beneficial for improving pain, disability, and quality of life in patients with cervical spondylodiscitis. Interventional pain management, targeting the source of pain with facet joint injections and trigger point injections, might offer a greater advantage in reducing pain and improving disability compared to medical treatment. However, larger, prospective studies are needed to confirm these findings and explore the role of advanced local methods. While surgery is becoming less frequent due to advancements in conservative management, it remains critically important and potentially lifesaving for a select group of patients. Further research is warranted to optimize treatment algorithms that integrate both conservative and surgical approaches for optimal patient outcomes.

Author contribution

Study conception and design: ÇY and AKÇ; data collection: ÇY and AKÇ; analysis and interpretation of results: OKD; draft manuscript preparation: ÇY and OKD. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Toros University (Protocol no. 123/27.10.2023).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

CASE REPORT

Axillary arch as a rare variant of the latissimus dorsi: cadaveric case report and literature review

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ABSTRACT

This case report explores the axillary arch, a rare anatomical variation of the latissimus dorsi muscle, which can compress vital neurovascular structures in the axilla. We present a detailed examination of a 75-year-old male cadaver, where the axillary arch was identified extending from the latissimus dorsi to the pectoralis major. The arch measured 6.0 cm in length and 0.6 cm in width, passing over the intercostobrachial nerve, median nerve, and medial brachial vein. The potential for this anatomical variant to cause neurovascular compression and contribute to conditions such as thoracic outlet syndrome is discussed. This study emphasizes the importance of recognizing the axillary arch in surgical practice to avoid complications during procedures involving the axillary region. Insights gained from cadaveric dissections are vital for enhancing our understanding of anatomical variations and their clinical implications.

Keywords: axillary arch, neurovascular compression, surgical anatomy, anatomical variation, cadaveric study

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INTRODUCTION

The axilla is a clinically significant region due to the presence of vital neurovascular structures and a variety of anatomical variations. One such variation is the axillary arch (AA), an anomaly of the latissimus dorsi muscle. This muscular slip typically extends from the anterior edge of the latissimus dorsi and crosses the axillary neurovascular bundle. Its insertion varies and may include the pectoralis major, coracoid process, biceps brachii, or brachial fascia.

The AA has been linked to potential neurovascular entrapment, especially in clinical or surgical settings. Cadaveric studies remain essential for identifying such variants. This paper presents a rare case in which the AA was observed to lie in close proximity to both the intercostobrachial and median nerves, as well as the brachial vein. Clinical implications of this variation are discussed, along with a literature review.

CASE PRESENTATION

During a dissection course at the Anatomy Laboratory of the Medical School, Aristotle University of Thessaloniki, we examined a 75-year-old male cadaver with no available medical history or known cause of death. The cadaver had been embalmed using a formalin-based technique. Dissection of the axillary region revealed an abnormal muscular structure.

The AA originated from the lateral border of the thoracic part of the latissimus dorsi muscle, had an oblique course from the medial inferior to lateral superior and inserted into the inferior deep surface of the pectoralis major muscle next to its insertion to the humeral bone. It was measured in cm, using a digital sliding caliper (Mitutoyo ABSOLUTE 500-196-20 model; Mitutoyo Corporation, Kanagawa, Japan), which had a recording of 6.0 cm in length and 0.6 cm in width. The landmarks that were used for the exact measurement of the Axillary Arch are

for the width we took the visible borders of the AA; however, for the length we took the origin of the arch on the upper third of the lateral border of the latissimus dorsi to the point where the arch inserted on the deep inferior surface of the pectoralis major, at its insertion to the bicipital groove The AA coursed obliquely over the axillary contents, traversing anterior to the intercostobrachial nerve (ICBN), the median nerve (MN), and the medial brachial vein (MBV) (Figure 1).

DISCUSSION

The axillary region contains vital neurovascular elements and demonstrates a range of muscular variations with potential clinical relevance. Among the most frequently encountered variations is the axillary arch (AA), also known as Langer's arch. This muscular, tendinous, or fascial slip typically originates from the anterior border of the latissimus dorsi and traverses the axillary fossa to insert into the pectoralis major, coracobrachialis fascia, or brachial fascia [1,2].

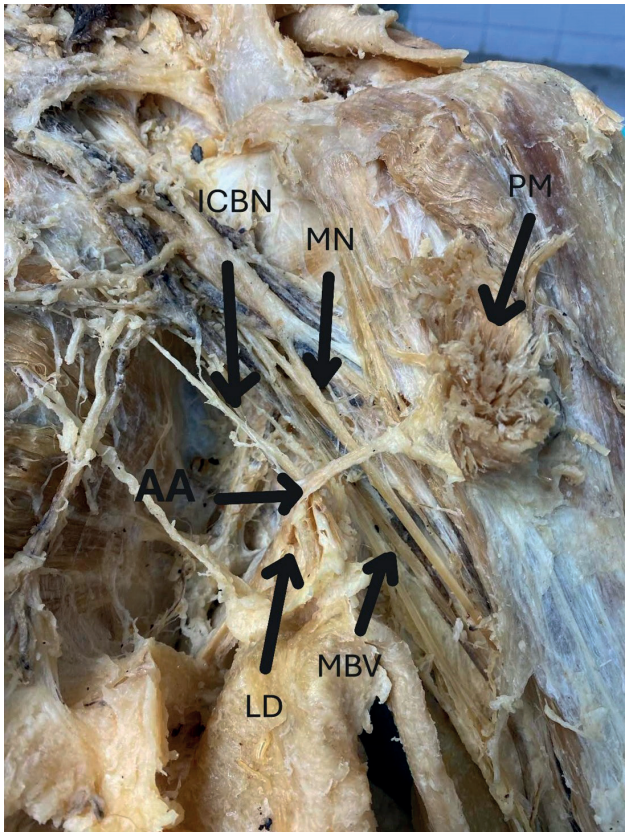

Figure 1. The AA originating from the latissimus dorsi (LD) and inserting into the pectoralis major (PM), lying superficial to ICBN, MN, and MBV. Bold arrows indicating the mentioned vessels, nerves, and muscles.

The AA may be complete or incomplete depending on its insertion pattern and may cross superficial or deep to the neurovascular bundle [3]. In our case, the AA coursed obliquely over the axillary contents, lying anterior to the intercostobrachial nerve, median nerve, and brachial vein. While no compression was documented, this anatomical configuration raises the possibility of dynamic impingement during arm movement [4].

Although frequently asymptomatic, the AA has been associated with thoracic outlet syndrome, venous stasis, lymphedema, and median or ulnar nerve entrapment in select clinical scenarios [5,6]. Some symptoms—such as axillary edema, venous dilation, or positional paresthesia—have been reported in relation to the AA, though establishing causality remains challenging in the absence of imaging or electrophysiological data [7].

The prevalence of the AA varies widely in the literature, ranging from 0.25% to 27% in cadaveric studies [8,9], and up to 43.8% in some imaging series [10]. The majority of cases are unilateral, with inconsistent data regarding lateralization. While Bertone et al. [11] reported a left-sided predominance, others found a higher frequency on the right [4]. Gender does not appear to influence prevalence significantly [9].

The AA's morphology is variable, with reported lengths ranging from 7–12.5 cm and widths of 0.6–1.5 cm [1,12]. In our case, the arch measured approximately 6.0 cm in length and 0.6 cm in width, inserting into the deep surface of the pectoralis major. Based on MRI studies, the AA may be visualized in coronal, axial, or sagittal planes, potentially mimicking masses during imaging or surgical procedures [13].

The arch may receive innervation from the thoracodorsal, medial, or lateral pectoral nerves and vascular supply from the lateral thoracic or pectoral arteries [2,14]. The intercostobrachial nerve, which provides cutaneous innervation to the medial upper arm and lateral thoracic wall, is particularly vulnerable to entrapment beneath such muscular variants [15].

In surgical contexts, failure to recognize the AA may result in incomplete lymphadenectomy, hemorrhage, or misidentification as a pathological mass during axillary clearance or breast cancer surgery [16]. Given the potential implications,

knowledge of this variation is essential for surgeons, radiologists, and anatomists alike.

Limitations

As this is a cadaveric case, there is no clinical history or imaging data available to confirm any actual neurovascular compression during life. The anatomical relationships observed suggest potential implications, but these remain speculative without clinical correlation. The absence of dynamic testing, electromyographic data, or patient history limits the ability to draw definitive conclusions regarding symptoms or functional impact.

CONCLUSION

The AA is a well-documented anatomical variant that may go unrecognized in both surgical and radiological contexts. In this case, the AA was found in close proximity to the ICBN, median nerve, and brachial vein, suggesting the possibility of neurovascular interaction during life.

Although no clinical symptoms can be confirmed, the awareness of such anatomical variations is essential for surgeons and radiologists to avoid misdiagnosis and surgical complications. Cadaveric studies remain a valuable tool in elucidating the presence and potential impact of these variants.

Author contribution

Study conception and design: CL, GP, and CC; data collection: CL, GP, and NA; analysis and interpretation of results: CL, GP, NA and GP; draft manuscript preparation: CL, GP and PG. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

No personal or identifiable information is included or disclosed in the study, and all procedures comply with ethical standards commonly applied to anatomical research.

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Conflict of interest

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acta medica

LETTER TO THE EDITOR

Thoracic vertebral metastasis and spinal cord injury secondary to multiple myeloma: a case report

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Dear Editor,

Multiple myeloma (MM) is a multisystemic B-cell malignancy characterized by clonal proliferation of plasma cells in the bone marrow [1]. The disease often leads to extensive skeletal involvement, resulting in severe pain, pathological fractures, and spinal cord compression2. Osteolytic bone lesions are among the most characteristic manifestations of MM and are present in nearly 80% of patients at the time of diagnosis. The axial skeleton—particularly the vertebrae—and the proximal regions of long bones are most commonly affected, although any bone may be involved [2,3]. The average life expectancy of MM patients remains approximately 2.5 years despite advances in therapy, and up to 75% of patients with spinal involvement die within the first year after diagnosis1. The presence of vertebral metastasis or compression fracture not only worsens the prognosis but also significantly impairs quality of life. Herein, we present the clinical course of a 61 year-old woman diagnosed with MM following thoracic vertebral metastasis, who developed spinal cord injury after surgery and underwent a comprehensive rehabilitation program.

A 61 year-old female patient presented to the Department of Physical Medicine and Rehabilitation with complaints of sudden-onset, progressively worsening, diffuse back pain. Her neurological examination revealed paravertebral muscle spasm. Thoracic magnetic resonance imaging (MRI) demonstrated a compression fracture at the ninth thoracic vertebra (T9) and metastatic lesions involving the T9 vertebral body (Figure 1) and the left sacroiliac joint. Based on these findings, she was referred to the Department of Orthopedics and Traumatology, where she underwent T9 corpectomy, T6–T12 plate and screw stabilization, and tumor resection. Histopathological examination revealed plasmacytoma. These results met the diagnostic criteria for MM. Postoperatively, the patient received both radiotherapy and chemotherapy. However, she subsequently developed paraplegia secondary to metastatic compression fracture and was re-admitted to our rehabilitation service.

On her detailed neurological examination, the patient had no motor loss in the upper extremities, while motor strength in all key muscles of the lower extremities was assessed as 1/5. Sensory testing revealed hypoesthesia and anesthesia below the T5 dermatome. Anal examination showed preserved deep and superficial anal sensation, although voluntary anal contraction was absent. Based on these findings, the patient's spinal cord injury was classified as T5, ASIA Impairment Scale B. A multidisciplinary rehabilitation program was initiated, including range of motion exercises, balance and coordination training, postural and transfer exercises, as well as strengthening of both upper and lower extremities. Urodynamic evaluation was performed, and clean intermittent

catheterization was initiated. In order to increase bladder capacity, the anticholinergic agent trospium chloride was prescribed, and baclofen was started for lower limb spasticity. The patient gradually achieved unsupported sitting balance and partial independence in transfers. Verticalization training for therapeutic purposes was implemented, and after meeting the main rehabilitation goals, she was discharged with partial recovery at the wheelchair level.

Bone disease remains the most important factor reducing quality of life in MM patients. The underlying mechanisms involve a disruption of the balance between osteoclastic bone resorption and osteoblastic bone formation, resulting in excessive bone destruction and poor healing1-3. Vertebral metastases represent the majority of cases leading to epidural spinal cord compression and spinal cord injury [4]. Surgical management should therefore aim to restore spinal stability and decompress neural structures. However, even after optimal surgical, chemotherapeutic, and radiotherapeutic interventions, residual neurological impairment is unfortunately common. For this reason, early and individualized rehabilitation is essential to minimize complications, prevent secondary musculoskeletal problems, and optimize residual function.

In the presented case, the patient developed paraplegia following surgical treatment for thoracic vertebral metastasis secondary to MM. The rehabilitation process was focused on achieving functional independence in daily activities and maintaining the highest possible quality of life within the limitations of her condition [5]. Despite the low one-year survival rate reported in MM patients with spinal involvement, this case highlights that a tailored rehabilitation program can substantially improve comfort, autonomy, and psychological well-being. Rehabilitation interventions addressing muscle strength, joint mobility, sitting balance, and neurogenic bladder and neurogenic bowel managements are particularly crucial in such patients. Moreover, careful coordination between oncologists, orthopedic surgeons, and rehabilitation specialists is vital to ensure continuity of care and to address the complex needs arising from both the malignancy and its complications [5,6].

In conclusion, MM-related pathological vertebral fractures and subsequent spinal cord injuries can severely impair patients' quality of life and render them bedridden if not properly managed [1,7]. Following surgical treatment, chemotherapy, and radiotherapy, evaluation and management by a Physical Medicine and Rehabilitation specialist are indispensable. Individualized rehabilitation programs should aim to enhance patients' independence, prevent secondary complications, and improve functional outcomes, even in the presence of limited life expectancy. Although survival in MM patients with spinal involvement remains poor, maintaining and improving quality of life through multidisciplinary rehabilitation must be a primary therapeutic goal [5,8].

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