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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Efficacy and Safety of Topical Dapsone Versus Topical Tetracycline in Mild to Moderate Acne Vulgaris: A Retrospective Analysis

Hafif ve Orta Şiddette Akne Vulgariste Topikal Dapsona Karşı Topikal Tetrasiklinin Etkinliği ve Güvenliği: Retrospektif bir Analiz

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ABSTRACT

Aim: *In this study, we compared the efficacy and side effects of topical 7.5% dapsone and 3% tetracycline in patients with mild and moderate acne.*

Material and Methods: *The hospital's clinical Ethics Committee approved the study. A total of 100 subjects aged 12–40 were enrolled in the study, and each group contained 50 subjects who applied to the dermatology clinic with the complaint of acne from 01.09.22 to 30.11.22, were diagnosed with mild and moderate acne and were treated with topical 7.5% dapsone or 3% tetracycline for at least 12 weeks.*

Results: *A statistically significant difference was found between the 2 groups regarding acne scores and lesion numbers at the end of the treatment (p=0.006 for acne score, 0.002 for open comedones and <0.001 for other types of lesions). There was also a significant difference between the 2 groups regarding patients with an acne score of 0 or 1 after 12 weeks of treatment (p=0.007). At the end of the first month, there was a difference between the 2 groups regarding erythema, dryness and burning/stinging side effects (respectively p=0.009, 0.009 and <0.001).*

Conclusion: *Our results suggest that topical 7.5% dapsone is effective in treating mild to moderate acne and is safe in terms of side effects compared to topical 3% tetracycline.*

Key words: *topical dapsone; acne and dapsone; tetracycline and dapsone; topical tetracycline*

ÖZET

Amaç: *Biz bu çalışmada hafif ve orta şiddetli akne hastalarında7,5 dapson ve3 tetrasiklin'in etkinlik ve yan etkilerini karşılaştırdık.*

Gereç ve Yöntem: *Çalışma hastanenin Etik Kurulu tarafından onaylandı. Çalışmaya sivilce şikâyetiyle 01,09,22–30,11,22 tarihleri arasında dermatoloji polikliniğine başvuran, hafif ve orta şiddetli akne tanısı alan ve tedavisinde7,5 dapson veya3 tetrasiklin kullanılan, 1240 yaş arasında, her grupta 50 hasta olacak şekilde toplam 100 hasta alındı.*

Bulgular: *İki grup arasında tedavi sonundaki akne skorları ve lezyon sayıları açısından istatistiksel anlamlı fark bulundu (akne skoru için p=0,006, açık komedonlar için 0.002 ve diğer tüm lezyon tipleri için <0,001). Aynı zamanda 12 haftalık tedavi sonunda akne skoru sıfır ve bir olan hastalar açısından da gruplar arasında anlamlı fark vardı (p=0,007). Tedavinin 1. ayının sonunda iki grup arasında eritem, kuruluk ve yanma/batma hissi açısından fark bulundu (sırasıyla p=0,009, 0.009 and <0,001).*

Sonuç: *Bizim sonuçlarımız hafif ve orta şiddetli akne tedavisinde topikal3 tetrasiklinle karşılaştırmada topikal7,5 dapsonun daha etkili ve yan etkiler açısından daha güvenli olduğunu göstermektedir.*

Anahtar kelimeler: *akne ve dapson; tetrasiklin ve dapson; topikal dapson; topikal tetrasiklin*

Introduction

Acne vulgaris (AV) is a chronic inflammatory disease of the hair follicle and sebaceous glands[1]. The prevalence of acne is 12% in women and 4% in men[2]. Since sebaceous glands are more common in places such as the face, pectoral region and back, acne is also an effective factor in social life and has psychological interactions[3]. Acne treatment can be summarized under 3 main headings as topical treatments, systemic antibiotics and systemic isotretinoin. Topical tetracycline has both antimicrobial and anti-inflammatory properties. Dapsone (4-amino 4-diphenyl sulfone), which

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shows its effect by competitively inhibiting dihydropteroate synthetase against para-aminobenchoic acid, is a drug from the sulfone group discovered in 1908 and has both anti-inflammatory and antimicrobial activity[4–6]. It is known to inhibit neutrophil chemotaxis by different pathways[7, 8]. This study compared the efficacy and side effects of topical 7.5% dapsone and topical 3% tetracycline in patients with mild and moderate AV.

Material and Methods

Ethics Approval

Our study was approved by the clinical research ethics committee.

Study Design

The study was conducted retrospectively by scanning patient files. The files of the patients aged 12–40 years who applied to the dermatology outpatient clinic with the complaint of acne between 01.09.2022 and 30.11.2022 were diagnosed with mild and moderate AV, had Investigator's Static Global Assessment (ISGA) scores between 2–4 and was treated with topical 7.5% dapsone or topical 3% tetracycline (drugs were administered only once a day) were included in the study. Those younger than 12 and older than 40 years, those with nodulocystic acne and severe acne, those who received other acne treatments and those who had facial treatments (energy-based device, peeling, dermabrasion, epilation, etc.) in the 3 months before the first examination, and those who used systemic corticosteroid, retinol-containing or acidic cosmetic products were not included in the evaluation. A hundred patient files were evaluated, with 50 patients in each group. In our study, we used information such as demographic characteristics in the patient files, ISGA scores before treatment and at the end of each month during 12 weeks of treatment, the number of non-inflammatory lesions, including open and closed comedones, the number of inflammatory lesions including papules and pustules, and side effects and severity scores (0-none, 1-mild, 2-moderate, 3-severe) at the end of each month control. Patients with an ISGA score of 0 or 1 at the end of treatment were considered "recovered patients" or "clinical success."

Examination of the patients, determination of the severity of the disease, treatment and follow-up were performed by the same doctor (S. H.). Treatment was not discontinued in any of the patients in the study due to side effects.

Statistics

Data were entered in the software IBM Statistical Package for Social Sciences (SPSS) program version 25 (IBM© Corp., Armonk, NY, USA) and this program was used for statistical analysis. Discontinuous variables were expressed in numbers and percentages, while continuous variables were expressed in mean +/– standard deviation. P value <0.05 was considered statistically significant. Chi-squared test was used to investigate independent variables for discontinuous variables. Whether the groups conformed to normal distribution in terms of continuous variables was assessed using the Kolmogorov-Smirnov test, and The Wilcoxon test was used when investigating dependent groups in terms of variables that did not conform to the normal distribution, and the Mann Whitney U test was used when investigating independent groups.

Results

A hundred patients were included in the study, with 50 patients in each group. The age was 23.94 +/– 7.78 years in the group using dapsone, while it was 22.70 +/– 8.38 years in the group using tetracycline. There were 32 male patients in the study, 19 (38%) in the dapsone group and 13 (26%) in the tetracycline group. There was no statistically significant difference between the groups regarding age and gender (p=0.357 and 0.198, respectively). Detailed demographic data are shown in Table 1.

Table 1. *Demographics and general data*

	Dapsone (n=50)	Tetracysline (n=50)
Age (years, mean ± sd)	23.94±7.78	22.70±8.38
Gender (n / %)		
Male	19/38	13/26
Female	31/62	37/74
Initial ISGA values (mean ± sd)	2.74±0.72	2.84±0.65
2 (n /%)	21/42	15/30
3 (n /%)	21/42	28/56
4 (n /%)	18/16	7/14
Initial NNL[1] (mean ± sd)	40.84±9.83	43.90±9.45
Open comedone	10.52±2.89	11.66±3.47
Closed comedone	30.32±7.10	32.24±6.38
Initial NIL[2] (mean ± sd)	35.58±6.29	37.84±7.48
Papule	13.24±1.76	13.84±2.39
Pustule	22.34±4.63	23.40±4.60
Initial TNL[3] (mean ± sd)	76.44±15.94	81.16±15.12

[1]NNL-Number of noninflammatory lesions, [2]NIL-Number of inflammatory lesions, [3]TNL-Total number of lesions.

Table 2. *Investigator's Static Global Assessment scores, clinical cure rates, lesion counts, and percentile reductions at the end of treatment*

mean ± sd	Dapsone	Tetracycline
ISGA	1±0.90	1.54±1.01
Percentage reduction	65±30.45	46±36.51
Clinical success (n / %)	38/76	25/50
NNL	9.30±10.56	18.30±10.13
Percentage reduction	78.43±22.93	57.36±24.64
Open comedone	3.08±3.15	5.10±3.38
Percentage reduction	72.62±26.54	56.16±27.03
Closed comedone	6.22±7.54	13.20±7.60
Percentage reduction	80.38±22.23	57.84±26.14
NIL	6.86±8.38	12.90±8.27
Percentage reduction	81.80±21.39	63.74±27.03
Papule	2.98±3.42	5.44±3.35
Percentage reduction	78.32±23.92	59.86±26.51
Pustule	3.84±5.19	7.46±5.41
Percentage reduction	83.97±20.95	65.85±29.57
TNL	16.16±18.81	31.20±17.60
Percentage reduction	79.99±22.04	60.61±24.21

There was no statistically significant difference between the 2 groups in terms of ISGA values, open and closed comedones, non-inflammatory lesions, papules, pustules, inflammatory lesions and total lesions before the treatment (p=0.400, 0.095, 0.181, 0.100, 0.111, 0.151, 0.066 and 0.091, respectively, Table 1).

When each group was investigated in terms of pre– and post-treatment ISGA values, open and closed comedones, non-inflammatory lesions, papules, pustules, inflammatory lesions and total lesion counts, statistically significant differences were found for each group separately in terms of ISGA values and all lesion types (p<0.001 for all).

When the 2 groups were compared in terms of ISGA values and percent decrease in ISGA values at the end of treatment, a statistically significant difference was found between the groups (p=0.006 and 0.005, respectively), and the decrease was greater in the dapsone group. Likewise, it was also examined whether there was a difference between the groups in terms of the number of lesions and the percentage decreases in the number of lesions, and a statistically significant difference was found between the groups (p=0.002 for open comedones, p<0.001 for others). The reduction in lesions was more common in the group using dapsone. Data on this subject are detailed in Table 2.

Patients with an ISGA score of 0 or 1 (recovered patient) after 12 weeks of treatment in each group were evaluated, and it was examined whether there was a difference between the groups in this respect. A statistically significant difference was found between the 2 groups regarding patients who recovered (p=0.007). The number of recovered patients who used dapsone was higher in the group. Details are given in Figure 1.

Table 3. *Side effect data at monthly checkups*

	Dapsone			Tetracycline		
n / %	End of 1st m	End of 2nd m	End of 3rd m	End of 1st m	End of 2nd m	End of 3rd m
Erythema	9/18	5/10	0/0	21/42	6/12	3/6
mild	4/8	5/10	0/0	6/12	4/8	3/6
moderate	3/6	0/0	0/0	5/10	1/2	0/0
severe	2/4	0/0	0/0	10/20	1/2	0/0
Dryness	9/18	3/6	0/0	21/42	5/10	3/6
mild	6/12	2/4	0/0	8/16	2/4	2/4
moderate	3/6	1/2	0/0	5/10	1/2	1/2
severe	0/0	0/0	0/0	8/16	2/4	0/0
Burning/stinging	8/16	5/10	1/2	26/52	9/18	3/6
mild	7/14	5/10	1/2	16/32	6/12	3/6
moderate	1/2	0/0	0/0	2/4	2/4	0/0
severe	0/0	0/0	0/0	8/16	1/2	0/0

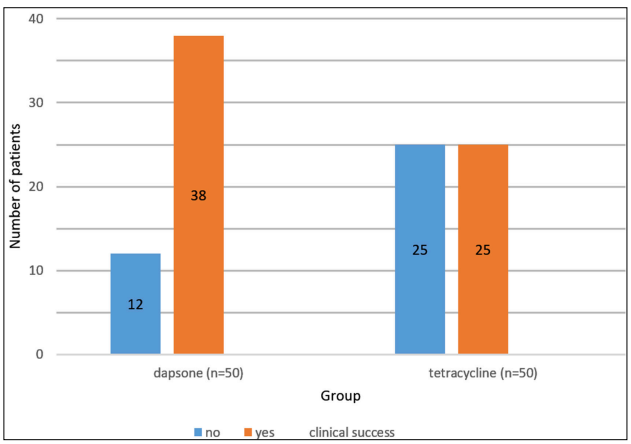

Figure 1. *Clinical success data by groups.*

When the 2 groups were evaluated in terms of erythema, there was a difference at the end of the 1st month (p=0.009, erythema was more common in the tetracycline group), there was no difference at the end of the 2nd month (p=0.749), and there was a difference at the end of the 3rd month (p=0.022, in the dapsone group no erythema was found). When the 2 groups were evaluated in terms of dryness side effects, it was found that there was a statistically significant difference between the groups at the end of the 1st month control (p=0.009, dryness was more common in the tetracycline group), but there was no difference in the 2nd and 3rd month controls (p=0.461 and 0.110, respectively). Considering whether there is a statistically significant

difference between the groups in terms of burning and stinging side effects, there is a statistically significant difference at the end of the 1st month ($p<0.001$); this side effect is more common in the tetracycline group), but there is no difference in the controls at the end of the 2nd and 3rd months ($p=0.249$ and 0.161, respectively). Data on side effects seen at monthly controls are detailed in Table 3.

When the patients with side effects in each group were compared in terms of severity of side effects, there was no statistically significant difference in terms of severity in patients with both erythema, dryness and burning/stinging at the end of the 1st and 2nd-month controls ($p=0.426$ and 0.361, respectively, in patients with erythema, $p=0.093$ and 0.449 in patients with dryness, $p=0.199$ and 0.346 in patients with burning/stinging). This comparison could not be made, as no erythema and dryness were observed in patients using dapsone at the end of the 3rd-month controls. Similarly, statistical comparison could not be made between the groups of patients using dapsone and patients who were burning/stinging since this side effect was very rare.

Discussion

There was no statistically significant difference between the two groups compared in our study in terms of demographic characteristics, pre-treatment ISGA scores and the number of lesions. When each group was evaluated in isolation, a statistically significant difference was found in ISGA values and the number of lesions before and after 12 weeks of treatment, and this shows that both treatment modalities are effective in treating mild and moderate acne separately. However, when the 2 groups are evaluated in terms of ISGA values and percentage reductions at the end of treatment, as well as the number of lesions and percentage reductions, it is seen that topical 5% dapsone is more effective than topical 3% tetracycline. When the 2 groups are compared in terms of side effects, it is observed that the side effects are less common in the group using dapsone, especially in the control at the end of the first month of treatment.

In the literature review, no previous studies of efficacy and side effects of topical 5% dapsone and topical 3% tetracycline were found. Most studies with topical dapsone have compared the drug to placebo.

Stein Gold LF[9], Eichenfield LF[10] evaluated 4340 AV patients in two randomized, double-blind controlled studies for once-daily use of 7.5% dapsone and placebo and they find a significant improvement in both ISGA values and the number of non-inflammatory and inflammatory lesions in the dapsone group at the end of 12 weeks of treatment.

Draelos et al.[11] showed that 5% dapsone used twice a day had a significant effect on acne scores compared to the control group (decrease of 40.5% and 32.8%, respectively) in a multicenter, 12-week, double-blind, randomized, phase 3 study in which 3010 individuals were evaluated. The study observed a significant decrease in non-inflammatory (32% and 24%) and inflammatory (47.5% and 41.8%) acne lesions in the dapsone group compared to the control group. In the follow-ups, they did not see any abnormality (even in those with G-6PD deficiency) in laboratory tests. Side effects such as 21.8% dryness, 20% erythema, 1.4% burning sensation, 1% itching and 0.1% irritation were observed in the dapsone group.

In a placebo-controlled, randomized study conducted by Gita Faghihi et al.[12], they investigated the efficacy and side effects between systemic 20 mg/day isotretinoin + 5% dapsone and systemic 20 mg/day isotretinoin + placebo in a 12-week treatment period in 58 patients with moderate and severe acne aged 18–25 years. While the decrease in the number of non-inflammatory and inflammatory lesions at the end of the treatment was significantly higher in the dapsone group than in the other group, no difference was found between the placebo group regarding a decrease in acne score. They found that the efficacy was greater in female patients. In the dapsone group, they observed a burning sensation in 7 patients (24.13%), mild erythema in 4 patients (13.79%), and mild dryness in 3 patients (10.34%). No abnormality was observed in hemoglobin levels in the follow-ups of the patients.

Lucky et al.[13] investigated the efficacy of 5% dapsone applied topically twice daily in a multicenter, 12-month phase 3 study, and at the end of the 12 th month, they observed a 58.2% decrease in inflammatory lesions, a 19.5% decrease in non-inflammatory lesions and a 49% reduction in the total number of lesions. Mostly mild application area side effects were observed in 13.8% of the patients ((2.9% dryness, 2.5% redness-rash, 2.3% sunburn, 1.6% stinging, 1.6% erythema and 1.4% itching).

Conclusion

When the results of our study and the other studies mentioned above are evaluated, it is suggested that topical dapsone is effective in treating mild and moderate AV and is safe regarding side effects compared to topical 3% tetracycline.

The authors do not recommend topical antibiotics for treating acne due to the risk of resistance development. However, topical antibiotics in combination with topical retinoids or topical benzoyl peroxide are recommended.

Limitations of the study

One limitation is the study's retrospective nature. Because the study was conducted in a specific country, that is, at a specific geographic latitude, the results cannot be generalized to the whole world. There were no severe acne patients in the study, so the results do not apply to severe acne. The results cannot be generalized to other age groups since the study was conducted on patients within the age group 12–40 only.

No supports were received for the study from any person and/or institution.

The study has no conflicts of interest (due to a single author).

All authors have approved this final version of the article and have given permission for it to be submitted to you for publication.

References

1. Zhou M, Yang M, Zheng Y, Dong K, Song L, He C, et al. Skin surface lipidomics revealed the correlation between lipidomic profile and grade in adolescent acne. J Cosmet Dermatol. 2020;19:3349–56.
2. Poli F, Auffret N, Leccia MT, Claudel J-P, Dréno B. Truncal acne, what do we know? J Eur Acad Dermatol Venereol. 2020;34:2241–6.
3. Dréno B, Araviiskaia E, Kerob D, Andriessen A, Anfilova M, Arenbergerova M, et al. Nonprescription acne vulgaris treatments: Their role in our treatment armamentarium-An international panel discussion. J Cosmet Dermatol. 2020;19:2201–11.
4. Wozel G, Blasum C. Dapsone in dermatology and beyond. Arch Dermatol Res. 2014;306(2):103–24.
5. Sago J, Hall RP. Dapsone. Dermatol Ther. 2002;15:340–51.
6. Paniker U, Levine N. Dapsone and sulfapyridine. Dermatol Clin. 2001;19:79–86, viii.
7. Schmitdt E, Reimer S, Kruse N, Bröcker EB, Zillikens D. The IL-8 release from human keratinocytes, mediated by antibodies to bullous pemphigoid autoantigen 180, is inhibited by dapsone. Clin Exp Immunol. 2001;124:157–62.
8. Wozel G, Lehmann B. Dapsone inhibits the generation of 5-lipoxygenase products in human polymorphonuclear. Skin Pharmacol. 1995;8:196–202.
9. Stein Gold LF, Jarratt MT, Bucko AD, Grekin SK, Berlin JM, Bukhalo M, et al. Efficacy and safety of once-daily dapsone gel, 7. 5% for treatment of adolescents and adults with acne vulgaris: first of two identically designed, large, multicenter, randomized, vehicle-controlled trials. J Drugs Dermatol. 2016;15(5):553–61.
10. Eichenfield LF, Lain T, Frankel EH, Jones TM, Chang-Lin J-E, Berk DR, et al. Efficacy and safety of oncedaily dapsone gel 7. 5% for treatment of adolescents and adults with acne vulgaris: second of two identically designed, large, multicenter, randomized, vehicle-controlled trials. J Drugs Dermatol. 2016;15(8):962–9.
11. Draelos ZD, Carter E, Maloney JM, Elewski B, Poulin Y, Lynde C, et al. Two randomized studies demonstrate the effi cacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. J Am Acad Dermatol. 2007;56:439.e1–10.
12. Faghihi G, Rakhshanpour M, Abtahi-Naeini B, Nilforoushzadeh MA. The effi cacy of 5% dapsone gel plus oral isotretinoin versus oral isotretinoin alone in acne vulgaris: A randomized double-blind study. Adv Biomed Res. 2014;3:177.
13. Lucky AW, Maloney MJ, Roberts J, Taylor S, Jones T, Ling M, et al. Dapsone gel 5% for the treatment of acne vulgaris: safety and efficacy of long-term (1 year) treatment. J Drugs Dermatol. 2007;6:981–7.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Knowledge Levels of Probiotics and Consumption Status of Probiotics and Prebiotics in Patients Applicant to the Gastroenterology Outpatient Clinic

Gastroenteroloji Polikliniğine Başvuran Hastalarda Probiyotik Bilgi Düzeylerinin ve Probiyotik ve Prebiyotik Tüketim Durumlarının Değerlendirilmesi

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ABSTRACT

Aim: *This study aims to evaluate the probiotic knowledge level and consumption status of patients who apply to gastroenterology outpatient clinics.*

Material and Methods: *The study was conducted at the gastroenterology outpatient clinic of Sakarya Training and Research Hospital between October 2020 and January 2021. The researcher filled out an interview form for patients who agreed to participate in the study. The interview included questions about patients' demographic data, probiotic knowledge, and consumption habits.*

Results: *66.52% (n: 230) of patients participating in the study were female, and the average age was 44.42 years. While 12 (5.22%) were illiterate, 106 (46.09%) were primary school graduates, 74 (32.17%) were secondary school graduates, 74 (14.78%) were university graduates, and 4 (1.74%) were post-graduates. Seventy-four (32.17%) of patients had at least one chronic disease, and 87 (37.82%) smoked an average of 15 cigarettes a day. When asked, "What is a probiotic? Do you know?" 161 (70.00%) of patients stated that they did not know this concept. Only 51 (22.17%) of patients were using probiotics. Patients obtained information about probiotics from 12 (17.39%) specialist doctors, 7 (10.14%) from friends and family, 28 (40.57%) from advertisements, 8 (11.59%) from training seminars, 11 (15.94%) from pharmacies, and 38 (55.07%) from the internet and social media. The probiotic foods consumed were kefir (n: 36, 70.58%), probiotic yoghurt. (n: 29, 56.86%), respectively. probiotic cheese (n: 11, 21.56%) and probiotic milk (n: 7, 13.72%). Ten (19.60%) of patients were using probiotic powder/tablets*

Conclusions: *In our study, we observed that the probiotic knowledge levels and consumption habits of the patients who applied to the gastroenterology outpatient clinic were low. Probiotics are important microorganisms for intestinal health and maintaining a healthy microbiota. Lack of information in patients causes low consumption of these beneficial microorganisms. Further studies are needed to improve the level of knowledge and consumption habits.*

Key words: *probiotic; knowledge level; consumption status; patient; gastroenterology outpatient clinic*

ÖZET

Amaç: *Bu çalışmanın amacı gastroenteroloji polikliniğine başvuran hastaların probiyotik bilgi düzeyi ve tüketim durumlarını değerlendirmektir.*

Gereç ve Yöntem: *Çalışma, 1 Ekim 2020–1 Ocak 2021 tarihleri arasında Sakarya Eğitim ve Araştırma Hastanesi gastroenteroloji polikliniğinde gerçekleştirildi. Çalışmaya başlamadan önce Sakarya Üniversitesi Tıp Fakültesi Etik Kurulu'ndan etik kurul onayı alındı. Çalışmaya katılmayı kabul eden hastalara araştırmacı tarafından görüşme formu dolduruldu. Görüşme formu, demografik veriler ile probiyotik bilgi ve tüketim alışkanlıklarına ilişkin bilgileri içeren sorulardan oluştu.*

Bulgular: *Çalışmaya katılan hastaların %66,52'si (n: 230) kadındı ve yaş ortalaması 44,42 yıldı. On ikisi (%5,22) okuryazar değilken; 106'sı (%46,09) ilköğretim, 74'ü (%32,17) ortaöğretim, 74'ü (%14,78) üniversite ve dördü (%1,74) yüksek lisans mezunuydu. Hastaların 74'ünün (%32,17) en az bir kronik hastalığı vardı ve 87'si (%37,82) günde ortalama 15 adet sigara içiyordu. "Probiyotik nedir? Biliyor musunuz?" diye sorulduğunda hastaların 161'i (%70,00) bu kavramı bilmediğini ve ilk kez duyduğunu bildirdi. Hastaların sadece 51'i (%22,17) probiyotik kullanıyordu. Hastalar probiyotikler ile ilgili bilgiyi, 12'si (%17,39) uzman doktordan, yedisi (%10,14) arkadaş ve aile bireylerinden, 28'i (%40,57) reklamlardan, sekizi (%11,59) eğitim-seminerlerden, 11'i (%15,94) eczanelerden ve 38'i (%55,07) internet ve sosyal medya aracılığıyla edinmişti. Tüketilen probiyotikli besinler sırasıyla, kefir (n: 36; %70,58), probiyotik yoğurt (n: 29, %56,86), probiyotikli peynir (n: 11, %21,56) ve probiyotikli süt (n: 7, %13,72) idi. Hastaların 10'u (%19,60) probiyotik toz/tablet kullanmaktaydı.*

Sonuç: *Çalışmamızda gastroenteroloji polikliniğine başvuran hastaların probiyotik bilgi düzeylerinin ve tüketim alışkanlıklarının düşük olduğu görüldü. Probiyotikler, bağırsak sağlığı ve sağlıklı bir mikrobiyotanın korunması için önemli mikroorganizmalardır. Hastalarda bilgi eksikliği bu faydalı mikroorganizmaların az tüketilmesine neden olmaktadır. Bilgi düzeyinin ve tüketim alışkanlıklarının iyileştirilmesi için daha fazla çalışmalara ihtiyaç vardır.*

Anahtar kelimeler: *probiyotik; bilgi düzeyi; tüketim durumu; hasta; gastroenteroloji polikliniği*

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Introduction

Gastrointestinal tract (GIS) health is directly related to the gut microbiota, which has an intact microbial ecosystem. The human gut microbiota includes indigenous gut microbiota that participate in various functions that improve host health[1]. Health maintenance depends on the gut microbiota, and microbial alterations can increase disease-causing pathogenic microorganisms[2]. Probiotic microorganisms are biotherapeutic products that maintain human health and reduce the risk of other metabolic disorders. FAO/WHO defines probiotics as "live microorganisms that provide health benefits to the host when administered in sufficient quantities"[3]. Probiotics primarily target the modulation of the intestinal microbiota to benefit the host's health[1].

Lactobacillus spp. and *Bifidobacterium spp., Saccharomyces spp., Bacillus spp., Escherichia coli, Enterococci* and *Weissella spp.* were reported to be the probiotic microorganisms used commercially in research and industry[4]. A global analysis of clinical studies with probiotics reported that the most studied probiotic strains were *Lactobacillus rhamnosus* GG (LGG) and *Bifidobacterium animalis ssp. lactis* BB12[5]. Many clinical studies have investigated probiotic bacteria (mainly lactobacillaceae and bifidobacteria) targeting various diseases and conditions[6]. Several species of the genera *Bifidobacterium* and *Lactobacillus* have been suggested to be beneficial to the gut microbiota by creating a favorable healthy environment in the gut. In high-quality meta-analyses, probiotics are effective against infectious diarrhea, antibiotic-associated diarrhea, traveler's diarrhea, slow bowel transit, irritable bowel syndrome, abdominal pain and bloating and ulcerative colitis[7,8].

Prebiotics are selectively fermented short-chain carbohydrates that stimulate the growth and activity of beneficial microbes colonizing the gut. Gibson and Roberfroid defined prebiotics as "a non-digestible food component that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thereby improving host health"[9]. Prebiotics contribute positively to the well-being and health of the individual by affecting the composition and activity of GI microorganisms[10].

Despite the availability of evidence and facilities supporting the use and health benefits of probiotics and prebiotics, there is still confusion surrounding these concepts[11]. Given that preventing dysbiosis and maintaining intestinal microbiota health is directly linked to overall health, patients seeking treatment at gastroenterology outpatient clinics must possess adequate knowledge about probiotics and prebiotics[12,13]. These substances play a significant role in safeguarding and enhancing intestinal microbiota health.

This study evaluated the probiotic knowledge level and consumption status of patients who applied to gastroenterology outpatient clinics.

Material and Methods

Place and time

The study, planned as a descriptive, was conducted at the gastroenterology outpatient clinic of Sakarya Training and Research Hospital (SEAH) between October 1, 2020 and January 1, 2021

Population and sample of the research

The study population consisted of patients who applied to the SEAH gastroenterology outpatient clinic between October 1, 2020, and January 1, 2021. The research used the convenience sampling technique. The sample consisted of 230 patients who agreed to participate.

Data collection tools

The researchers created the interview form by scanning the literature. It consists of two sections and 27 questions: sociodemographic information, level of knowledge about probiotics and prebiotics, and consumption habits.

Participant approval

The researcher informed patients who applied to the outpatient clinic about the study. Patients who agreed to participate in the study were included after filling out the informed consent form.

Collection of data

The researchers collected study data through face-to-face interviews. The interview form was filled out by the researchers for the patients who agreed to participate in the study, and each patient's interview lasted approximately 8 minutes.

Ethics committee approval

Before starting the study, ethics committee permission was obtained from the Sakarya University Faculty of Medicine Ethics Committee (dated 11.09.2020; number E-71522473-050.01.04-516).

Evaluation of Data

Data analysis was performed using Statistical Package for Social Sciences (SPSS) program version 22 for Windows (IBM Corp., Armonk, NY, USA). The study data are displayed as Frequency distributions (number, percentage) for categorical variables and descriptive statistics (mean, standard deviation, median, interquartile range) for numerical variables.

Results

Demographic data

Of the 230 study participants, 153 (66.52%) were female, 77 (33.48%) were male, and the average age was 44.42±14.10 years. Data regarding the sociodemographic information of the patients are shown in Table 1. 74 (32.17%) of the patients had at least one chronic disease, and 31 (13.47%) were constantly using medications due to these diseases. When patients' smoking habits were questioned, 87 (37.82%) of them had been smoking an average of 15 cigarettes a day for 20 years. When the distribution of patients is evaluated according to body mass index (BKI), 13 (5.65%) of the patients were underweight, 82 (35.65%) were normal, 79 (34.34%) were overweight, 51 (22.17%) were obese, and 5 (2%) were obese. 17) were severely morbidly obese (Table 1).

Data on probiotic information

When the findings regarding probiotic knowledge are evaluated, "What is probiotic? Do you know?" When the question was asked, 161 (70.00%) of the patients stated that they did not know and heard this concept for the first time, and 69 (42.85%) stated that they did not know what probiotic microorganisms were. Patients who knew about probiotics (30.00%) reported that probiotic microorganisms included yeast (27.53%), mold (24.63%) and lactobacilli (1.44%). While expressing that he knows, none of the patients stated that they knew about bifidobacter and streptococcus. When the sources of information about probiotic foods were evaluated, 12 (11.53%) of the patients obtained information from specialist doctors or dieticians, 7 (6.73%) from friends, relatives, family etc., 28 (26.92%) from advertisements, 8 (7.69%) from training, conferences and scientific meetings, 11 (10.57%) from pharmacies and sales points and 38 (36.53%) from the internet-social media (Table 2). Of the patients who knew about probiotics, 63 (91.30%) thought that probiotic foods positively affected health.

Information on Probiotic Consumption

When probiotic consumption habits were evaluated, it was found that only 51 (22.17%) of the patients consumed probiotics. The patients' reasons for consuming or not consuming probiotics and other information regarding probiotic consumption are presented in Table 2. The probiotic foods consumed by the patients were, respectively, kefir (n: 36; 70.58%), probiotic yoghurt (n: 29, 56.86%), probiotic cheese (n: 11, 21.56%) and probiotic milk (n: 7, 13.72%) (Figure 1). Ten (19.60%) of the patients were using probiotic powder/tablets. Patients reported that probiotic foods caused constipation (n: 28, 54.90%), diarrhea (n: 11, 21.56%), irritable bowel syndrome (n: 5, 9.80%), lactose intolerance (n: 3, 5%) inflammatory bowel diseases (n: 3, 5.88%), high cholesterol (n: 3, 5.88%), urogenital infections (n: 1, 1.96%), Helicobacter pylori infection (n: 1, 1.96%) stated that it was good for their diseases and 17 (33.33%) stated that it was good for the digestive system. Fifty-one (100%) of the patients using probiotics reported that they would recommend them to their close circle to consume probiotics. The answers given by the patients regarding the consumption of prebiotic and probiotic foods are shown in Figure 2.

Discussion

Our study evaluated the probiotic and prebiotic knowledge level and consumption status of patients who are applicants to the gastroenterology outpatient clinic. In our study, it was found that the level of knowledge of probiotics among patients was 30%. In the study conducted by Koray in our country to investigate the use and knowledge levels of probiotics in gastroenterology polyclinics and clinical patients, it was determined that 42% of the patients knew the concept of probiotics[14]. The study conducted by Ozdemir in the gastroenterology polyclinic of Sanko University Sani Konukoğlu Practice and Research Hospital reported that the rate of gastroenterology patients knowing the concept of probiotics correctly was 42.7%[15]. In a study conducted in the United Arab Emirates, it was

Table 1. *Sociodemographic characteristics of the patients*

Features		N (%) / Arithmetic mean ± standard deviation (minimum value-maximum value)
Age		44.4 ± 14.1 (18.0-78.0)
Gender	Female	153 (66.5)
	Male	77 (33.4)
Education status	illiterate	12 (5.2)
	Primary education	106 (46.0)
	Secondary education	74 (32.1)
	University	34 (14.7)
	Master degree	4 (1.7)
Job	Housewife	104 (45.2)
	Employee	60 (26.0)
	Retired	30 (13.0)
	Public employee	10 (4.3)
	Not working	10 (4.3)
Income status	Monthly income (TL)	3250.7 ± 948.9 (750-10.000)
Presence of chronic disease	Yes	74 (32.1)
	No	156 (67.8)
Distribution of chronic diseases	Hypertension	31 (33.3)
	Cardiovascular disease	7 (7.5)
	Diabetes mellitus	23 (24.7)
	Chronic obstructive pulmonary disease (COPD)	4 (4.3)
	Asthma	14 (15.0)
	Hypothyroidism	5 (5.3)
	Kidney failure	2 (2.1)
	Neurological diseases	4 (4.3)
	Hematological diseases	2 (2.1)
	Rheumatic diseases	1 (1.0)
Continuous drug use	Yes	31 (13.4)
	No	199 (86.5)
Distribution of drugs used	Antidiabetic	5 (10.8)
	Antihypertensive	8 (17.3)
	Proton Pump Inhibitor (PPPI)	7 (15.2)
	Antidepressant (SSRI)	4 (8.7)
	Antihistamine	2 (4.3)
	Antithyroid	2 (4.3)
	Anticoagulant	3 (6.5)
	Antiepileptic	2 (4.3)
	Laxative	2 (4.3)
	Anti-inflammatory	3 (6.5)
	Alphablockers	1 (2.1)
	Steroid	1 (2.1)
	Monoclonol antibody	1 (2.1)
	Antacid	1 (2.1)
	Bronchodilator	1 (2.1)
	Antispasmolytic	1 (2.1)
	Vitamin B12	1 (2.1)
	Iron	1 (2.1)
Body mass index (BMI) km/m^2 distribution	<18.5 underweight	13 (5.6)
	18.5-24.9 is normal	82 (35.6)
	25-29.9 overweight	79 (34.3)
	30-39.9 obese	51 (22.1)
	>40 severely morbidly obese	5 (2.1)
Smoking	Yes	87 (37.8)
	No	143 (62.1)
	Pieces (day)	14.9±6.7 (2.0-40.0)
	Duration (year)	20.5±11.6 (1.0-50.0)

Table 2. *Information on patients' probiotic knowledge and consumption habits*

Features		N (%)
Knowing probiotics	Yes	69 (30.0)
	No	161 (70.0)
Knowing the types of probiotic bacteria*	*Lactobacillus* species	1
	Bifidobacterium species	0
	Streptococcus species	0
	Yeasts	19
	Molds	17
	I don't know any of them - I haven't heard of them	161
Reasons to consume probiotic foods*	I saw its benefits for my digestive system.	40 (78.4)
	Because it regulates the gastrointestinal system	37 (72.5)
	I think it protects against cancer	7 (13.7)
	I find it delicious	7 (13.7)
	Strengthens the immune system	16 (31.3)
Reasons for not consuming probiotic foods	I do not know what it is	161 (89.9)
	I don't find it natural	0
	I don't need	11 (6.1)
	I find it expensive	0
	I find it tasteless	3 (1.6)
Where did you hear about probiotic foods?*	Specialist (Doctor or Dietician)	12 (23.5)
	Friend, acquaintance, family, etc.	7 (13.7)
	Advertisements (Newspaper, magazine, television)	28 (54.9)
	Education, conference, scientific meeting	8 (15.6)
	Pharmacies and sales points	11 (21.5)
	Internet-social media	38 (74.5)
What health benefits have you seen from probiotic foods?*	It was good for my cardiovascular diseases (high blood pressure, palpitations, etc.)	4 (7.8)
	Good for Digestive System Problems (constipation, diarrhea, etc.)	45 (88.2)
	It contributed to strengthening my immune system	21 (41.1)
	Depression, anxiety etc. It was good for my problems like	3 (5.8)
	It was good for my infectious diseases (cold, flu, etc.)	5 (9.8)
How TV, radio, newspapers and advertisements affect your probiotic food consumption*	Positive	35 (68.6)
	Negative	0
	Does not affect	16 (31.3)
Criteria you pay attention to when purchasing probiotic food*	Price	7 (13.7)
	Brand	22 (43.1)
	Nutrition label, content	38 (74.5)
	Appearance	1 (1.9)
Probiotic product consumption frequency*	1 time per day	22 (43.1)
	2-3 times a day	7 (13.7)
	1 time per week	14 (27.4)
	1-3 times a month	8 (15.6)
The amount of probiotic food you consume at a time*	½ (half) glass of water	5 (9.8)
	1 cup	46 (90.1)
Use of products containing probiotic powder or tablets*	Yes	10 (19.6)
	No	41 (80.4)
Have you benefited from probiotic foods?*	Yes	45 (88.2)
	No	6 (11.7)
Which diseases did consuming probiotic foods help you with?*	Constipation	28 (54.9)
	Diarrhea	11 (21.5)
	Allergy	0
	Lactose intolerance	3 (5.8)
	Inflammatory bowel diseases	3 (5.8)
	High cholesterol	3 (5.8)
	Urogenital infections	1 (1.9)
	Irritable bowel syndrome	5 (9.8)
	Helicobacter pylori infection	1 (1.9)
	Acute pancreatitis	0
	It was good for the digestive system	17 (33.3)
Would you recommend your friends to consume probiotic foods?*	Yes	51 (100)
	No	0

*Individuals who consume probiotics (n:51) and Patients answered these questions by selecting multiple options.

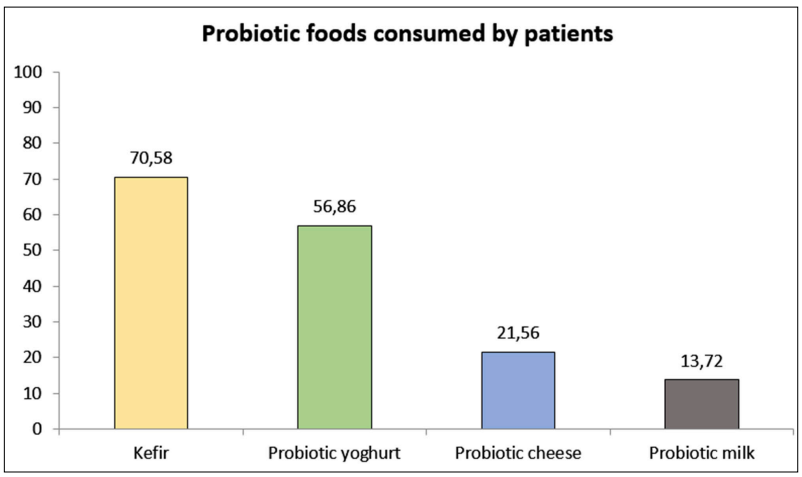

Figure 1. *Probiotic foods consumed by patients.*

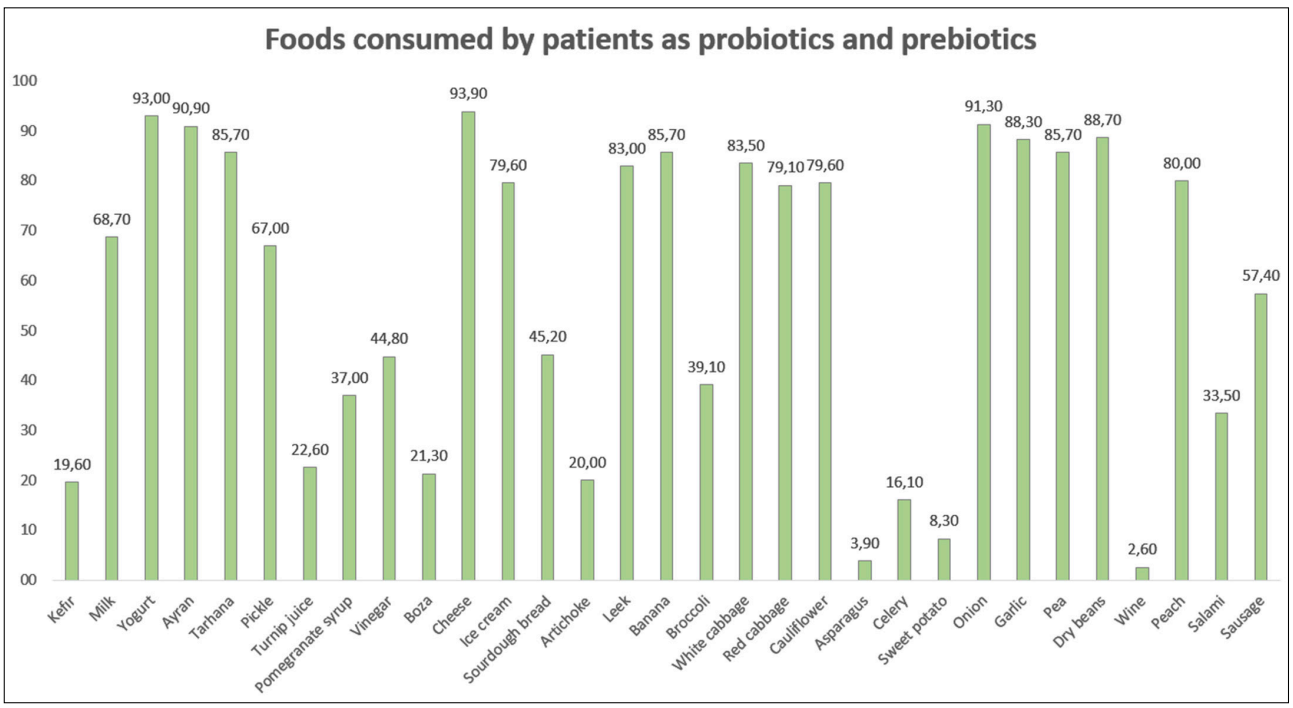

Figure 2. *Information on patients' consumption of prebiotic and probiotic foods.*

reported that 38.8% (n=64) of individuals could identify probiotics[16]. A study conducted with people living in Afyonkarahisar province stated that 46.8% of individuals knew about probiotics[17]. The study conducted by Şengün et al. in Izmir/Bornova showed that 49% of consumers knew the concepts of probiotic and prebiotic[18]. In the study conducted by Kağan et al., it was reported that 64.5% of adults knew the concept of probiotics[19]. In Aslantürk's study with individuals applying to the nutrition and diet clinic, it was found that 85% of the participants knew the term probiotic[20]. In a study conducted by face-to-face interview method with 25 participants to determine the knowledge level and consumption status of individuals in working life about probiotic foods, it was reported that 96% of the participants knew the term probiotic[21]. A study conducted with university students stated that 49.5% of the students knew about probiotics[22]. It has been observed that gastroenterology patients' knowledge of probiotics is low compared to the literature.

In our study, 27.53% of the patients knew yeast, 24.63% knew mold, and 1.44% knew lactobacilli. It was observed that none of the patients knew about bifidobacter and streptococcus. In the study conducted

by Aslantürk, 8.0% of the individuals knew about yeasts and 72% about probiotic bacteria[20]. In the study conducted by Ozgül, it was stated that 60% of the participants knew yeasts, 60% knew *Lactobacillus* species, 44% knew *Escherichia* species, 44% knew molds, and 8% knew *Bifidobacterium* species[21]. A study found that 69.4% of consumers did not know any probiotic microorganisms; the most known microorganism was Streptococcus spp. It was found to be (8.2%)[18]. Our study observed that knowledge about probiotic microorganisms was low, and this result was compatible with the literature.

It was determined that the probiotic consumption status of patients applying to the gastroenterology outpatient clinic was 22.60%[23]. A study conducted at the Columbia University Irving Medical Center Endoscopy unit found that 27% of gastroenterology patients used probiotics. A study conducted at a tertiary medical center in California found that 55% of patients had recently used probiotics. In the same study, it was reported that women were more likely to consume probiotics than men (odds ratio (OR): 1.99; 95% confidence interval (CI): 1.2–3.4)[24]. A study conducted to examine the knowledge and consumption levels of probiotics in patients who applied to the gastroenterology outpatient clinic at a university hospital in our country reported that 46.3% of the patients were careful to use probiotics. Still, only 7% of them used probiotic supplements[15]. The study conducted to determine the consumption habits of probiotic products reported that the rate of consumers consuming probiotic products was 26.0%[17]. Kağan et al. reported the probiotic consumption status of adult individuals as 73.6%[20]. In the study conducted to determine the knowledge level and consumption status of adult individuals about probiotic foods, it was reported that the probiotic food consumption status of individuals was 97.0%, the probiotic supplemented food consumption status was 44%, and the probiotic nutritional supplement usage status was 11%[21]. In the study conducted at Pamukkale University, 73.5% of the students were found to consume probiotic foods, and in the study conducted at Gümüşhane University, 82.4% of the students consumed probiotic foods[25,26]. A study conducted at Sakarya University Faculty of Engineering reported that 32.16% of Food Engineering Department students and 12.18% of chemistry students consumed probiotic food[27]. Another study investigating probiotic food consumption status reported that 56.3% of university students consumed probiotic foods[28].

Our study determined that the patients consumed probiotics mostly because they were beneficial to the digestive system and regulated the stomach-intestinal system. In their study, Lynch et al. reported that gastroenterology patients consumed probiotics because they improved general health and longevity and improved gastrointestinal symptoms[18]. In a study conducted with patients who applied to the gastroenterology outpatient clinic in our country, the patients stated that they used probiotics because they positively affected their intestines and liked their taste[15]. In the study conducted by Aslantürk, it was reported that the most common reasons adults consume probiotics are because they are beneficial to the digestive system (70.1%) and strengthen the immune system (48.5%)[21]. Another study conducted with adults found that 42% of individuals consumed probiotics for advice, 28.4% for health problems, 12.3% for the effect of advertisements, and 17.3% for other reasons[20]. In the study conducted with consumers, it was stated that 63.9% of the consumers thought that probiotics were beneficial to the digestive system, 19.5% thought that they were protective against cancer, 49.1% found them delicious, 49.1% thought that they strengthened the immune system, and 13% consumed probiotics due to the influence of advertisements[19]. In the study conducted by Zemzemoğlu et al. with university students, it was determined that 51.6% of the students consumed probiotics upon recommendation, 24.6% due to health problems and 11.8% due to the influence of advertisements[26]. The results of our study are compatible with the literature, and it has been observed that the most common reason for probiotic consumption is that it is beneficial to the digestive system.

When the reasons for not using probiotics were evaluated, it was determined that most gastroenterology patients in our study (89%) did not know what probiotics were. Fewer did not consume probiotics because they did not need them (6%) and found them tasteless (1%). In the study conducted by Ozdemir with patients who applied to the gastroenterology outpatient clinic, the reasons why the participants did not consume probiotics were as follows: they did not know what probiotics were (51%), they did not need them (25%), they found them expensive (18%), they did not believe they were effective (3%), and they did not taste them. It has been reported that people do not consume probiotics because they do not like them (1%)[15]. Another study conducted with adults reported that individuals did not consume probiotics because they did not know

what they were and found them tasteless[21]. In the study conducted by Ozgül et al. with individuals in working life, it was shown that individuals did not consume probiotics because they were not natural (50%) and did not need them[22]. According to the research results, the most common reason for not consuming probiotics is not knowing what probiotics are. The results of our study support the literature.

It was observed that the probiotic foods consumed by the patients were kefir, probiotic yoghurt, probiotic cheese and probiotic milk, respectively. Ten (19%) patients were using probiotic powder/tablets. As for natural probiotic foods, it was observed that the patients mostly consumed yoghurt, cheese and ayran. In the study conducted by Lync et al. with general gastroenterology patients, 33 of the patients consuming probiotics preferred prescribed probiotics, 9 preferred yoghurt, 7 preferred multiple probiotic products, 2 preferred kombucha, and 1 preferred a named bacteria; 78 of the patients reported that they were not sure about the type of probiotic they used[18]. In a study conducted in our country, when the consumption frequency of natural probiotic foods in gastroenterology patients was examined, it was determined that the food consumed at the highest rate every day was cheese, and the second most consumed food was pickled olives[15]. In the study conducted by Tenekeci, in which the use of probiotics and their knowledge levels were investigated in gastroenterology outpatient clinic and clinic patients, 134 of the patients consumed yoghurt, 75 consumed pickles, 38 consumed sourdough dough, 33 consumed fermented milk drinks such as kefir and probiotic drinks, and 9 consumed fermented milk drinks such as kefir and probiotic drinks. It was determined that 100 people used boza, 6 used probiotic food supplements and 21 used other probiotic products[14]. In the study conducted with consumers, it was determined that the most probiotic consumption distribution of consumers was kefir (51%), probiotic yoghurt (49.5%) and probiotic cheese (12.2%), respectively[19]. In the study conducted by Celik et al., the main products consumed by consumers most frequently were cheese, yoghurt, buttermilk, apple cider vinegar, cucumber/sauerkraut, respectively, while probiotic supplements, boza, and kombucha were determined to be the least consumed products[29]. In the study conducted by Ozgül et al., 20% of individuals in working life who use probiotic powders, capsules, pills, etc., have been reported to use[22]. When the literature was evaluated, it was seen that the most consumed probiotic product was yoghurt, and our study results are compatible with the literature.

When the probiotic information sources of the patients were evaluated, 12 (23.52%) of the patients came from specialist doctors, 7 (13.72%) from friends and family acquaintances, 28 (54.90%) from advertisements, 8 (15.68%) from advertisements obtained information about probiotics from training-seminars, 11 (21.56%) from pharmacies, and 38 (74.50%) from the internet-social media. A study reported that 20 patients had sources of probiotic information from TV, 3 from the internet, 15 from a dietician/doctor, 2 from newspapers/magazines, 9 from family/friends and 7 from other information sources[14]. In another study, gastroenterology patients' sources of information about probiotics were 16.3% TV commercials, 13.3% dietitians, 12.3% internet/social media, 7.3% doctors, 6.7% neighbor/friend, and 5.6%. It was reported that 3.7% were nutrition books, 3.7% were pharmacists, and 3.3% were other information sources[15]. In the research conducted on adult individuals' knowledge and consumption of probiotic foods, probiotics were consumed by advertisements (32.4%), friends-family-acquaintances (27.0%), specialist-dietitians-doctor (21.6%), and conferences, respectively. It was reported that he heard about it from scientific meetings and pharmacy sales points (9.5%)[20].

Our study determined that probiotic food consumption was mostly beneficial for health problems such as constipation (54.90%) and diarrhea (21.56%) in the patients. The study conducted with consumers found that it was good for constipation in 68.6% of the consumers, diarrhea in 42.3%, allergies in 16.7%, and the rate of being good for lactose intolerance was 12.2%[29]. In a study conducted with individuals in working life, probiotics were reported to be good for problems to reduce constipation (84%), diarrhea (60%), bloating and indigestion (52%), inflammatory bowel disease (36%), allergy and immune system (28%), and high cholesterol (4%)[22]. When the literature was examined, it was concluded that probiotics were mostly good for digestive system problems such as constipation and diarrhea. The results of our study are compatible with the literature.

The study's limitations include being conducted in a single city and a single center, and the majority of the patients participating in the study are female. When the literature is examined, it is seen that there are few studies on gastroenterology patients and probiotic consumption. Our study is original research that will

contribute to the literature in this respect and shed light on future studies.

Conclusion

Although studies on the benefits of probiotics are still ongoing, it is stated that the results for human health are positive. With the discovery of new probiotics and the use of probiotic strains in diseases, it will be possible to protect human health, treat diseases or prevent diseases. In our study, it was observed that gastroenterology patients had a low level of knowledge about probiotics and probiotic consumption. Considering gastroenterological diseases and their benefits to the digestive system and immune level, it is noteworthy that gastroenterology patients have low probiotic knowledge and low probiotic consumption. Activities such as training, projects, panels and seminars should be organized to increase the knowledge level and awareness of patients and their consumption habits and to explain probiotics and their beneficial effects that encourage healthy nutrition. Patients should be informed about probiotic consumption by being advised to apply to the outpatient clinic. Although studies in the field of gastroenterology regarding the knowledge and consumption levels of probiotics are limited, contributing to the literature by conducting clinical and descriptive studies in this field will shed light on future research. A limited number of studies have been conducted on this subject; more detailed studies are needed.

Acknowledgments

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Ethics Committee Approval

The research received ethics committee approval from the Sakarya University Faculty of Medicine Ethics Committee (dated 11.09.2020; number E-71522473-050.01.04-516).

Participant approval

The researcher informed patients who applied to the outpatient clinic about the study. Patients who agreed to participate in the study were included after filling out the informed consent form.

Peer Review

Externally peer-reviewed.

Author Contributions

Conception/Design of Study– GK, CK, ŞT; Data Acquisition– GK and CK; Data Analysis/Interpretation– GK and ŞT; Drafting Manuscript– GK and ŞT; Critical Revision of Manuscript– GK, ŞT, CK; Final Approval and Accountability– GK, ŞT and CK; Material and Technical Support– GK and CK; Supervision– GK and ŞT.

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

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References

1. Terpou A, Papadaki A, Lappa IK, Kachrimanidou V, Bosnea LA, Kopsahelis N. Probiotics in Food Systems: Significance and Emerging Strategies Towards Improved Viability and Delivery of Enhanced Beneficial Value. Nutrients. 2019;13;11(7):1591.
2. Yadav M, Shukla P. Recent systems biology approaches for probiotics use in health aspects: a review. 3 Biotech. 2019;9(12):448.
3. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11(8):506–14.
4. Kota RK, Ambati RR, Y V V AK, Srirama K, Reddy PN. Recent Advances in Probiotics as Live Biotherapeutics Against Gastrointestinal Diseases. Curr Pharm Des. 2018;24(27):3162–3171.
5. Dronkers TMG, Ouwehand AC, Rijkers GT. Global analysis of clinical trials with probiotics. Heliyon. 2020;17;6(7):e04467.
6. Duboux S, Van Wijchen M, Kleerebezem M. The Possible Link Between Manufacturing and Probiotic Efficacy;a Molecular Point of View on Bifidobacterium. Front Microbiol. 2021;4;12:812536.
7. Fijan S, Frauwallner A, Varga L, Langerholc T, Rogelj I, Lorber M, et al. Health Professionals' Knowledge of Probiotics: An International Survey. Int J Environ Res Public Health. 2019;28;16(17):3128.
8. Hasosah M, Qurashi M, Balkhair A, Alzahrani Z, Alabbasi A, Alzahrani M, et al. Knowledge, attitudes, and understanding of probiotics among pediatricians in different regions of Saudi Arabia. BMC Med Educ. 2021;21;21(1):68.
9. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr. 1995;125(6):1401–12.

10. Köse B, Aydın A, Özdemir M, Yeşil E. Determining the knowledge level and consumption status of healthcare professionals about probiotics, prebiotics and synbiotics. Academic Journal of Gastroenterology. 2019;18(2):67–72.
11. Deehan EC, Al Antwan S, Witwer RS, Guerra P, John T, Monheit L. Revisiting the Concepts of Prebiotic and Prebiotic Effect in Light of Scientific and Regulatory Progress-A Consensus Paper From the Global Prebiotic Association. Adv Nutr. 2024;15(12):100329.
12. Al-Habsi N, Al-Khalili M, Haque SA, Elias M, Olqi NA, Al Uraimi T. Health Benefits of Prebiotics, Probiotics, Synbiotics, and Postbiotics. Nutrients. 2024;16(22):3955.
13. Maftei NM, Raileanu CR, Balta AA, Ambrose L, Boev M, Marin DB, et al. The Potential Impact of Probiotics on Human Health: An Update on Their Health-Promoting Properties. Microorganisms. 2024;12(2):234.
14. Koray T. Investigation of probiotic use and knowledge levels in gastroenterology outpatient clinic and clinic patients (Master's thesis, Institute of Health Sciences). Ankara, 2018.
15. Ozdemir M. Knowledge levels and consumption frequencies of probiotics among those who applied to the gastroenterology outpatient clinic of Sanko University Sani Konukoğlu Practice and Research Hospital. (Master's thesis, Institute of Health Sciences). Kayseri, 2019.
16. Barqawi HJ, Adra SF, Ramzi HR, Abouaggour MA, Almehairi SK. Evaluating the knowledge, attitudes and practices of the UAE community on microbiota composition and the main factors affecting it: a cross-sectional study. BMJ Open. 2021;17;11(8):e047869.
17. Aslan S, Kara R, Yaman H. Determining the Consumption Habits Related to Probiotic Products. Turkish Journal of Agriculture - Food Science and Technology. 2019;7(6):861–865.
18. Lynch E, Troob J, Lebwohl B, Freedberg DE. Who uses probiotics and why? A survey study conducted among general gastroenterology patients. BMJ Open Gastroenterol. 2021;8(1):e000742.
19. Sengün İY, Kırmızıgül A, Özaydın İ, Yarım H. Determination of consumers' knowledge levels and consumption status regarding probiotic and prebiotic foods: İzmir/Bornova Example. GIDA/ The Journal of FOOD. 2020;45(1):103.
20. Kağan DA, Özlü T, Yurttaş H. A research on adult individuals' knowledge and consumption of probiotic foods. European Journal of Science and Technology. 2019;(17):556–563.
21. Aslantürk A. Determining the knowledge level and consumption status of adult individuals about probiotic foods (Master's thesis, Lisansüstü Eğitim Enstitüsü). İstanbul, 2019.
22. Ozgül AA, Bozat C, Seziş M, Badur Y, Özcan ÖÖ, Sarıyer ET, et al. Determining the Knowledge Level and Consumption Status of Individuals in Working Life About Probiotic Foods. Istanbul Gelişim University Journal of Health Sciences. 2020;(12):365–378.
23. Erdem N, Derin ÖD. Determınatıon Of Probıotıc Food Consumptıon Habıts Of Universıty Students: The Example of Selcuk University. Gümüşhane University Journal of Health Sciences. 2018;7(1):87–93.
24. Draper K, Ley C, Parsonnet J. A survey of probiotic use practices among patients at a tertiary medical centre. Benef Microbes. 2017;30;8(3):345–351.
25. Horasan, B. Determination of knowledge level and attitudes about probiotic foods among Pamukkale University students (Master's thesis, Pamukkale University Institute of Health Sciences). Denizli, 2021.
26. Zemzemoğlu TEA, Uludağ E, Uzun S. Determination of probiotic knowledge level and consumption status of university students. The Journal of Food. 2019;44(1):118–130.
27. Kanak EK, Yılmaz SÖ, Özacar ZZ, Uflas B, Bilek M, Yılmaz B. Evaluation of the Consciousness Levels of Food Engineering and Chemistry Department Students on Probiotic Food. Akademik Gıda. 2022;20(1):71–79.
28. Zemzemoğlu TEA, Uludağ E, Uzun S. Determination of probiotic knowledge level and consumption status of university students. The Journal of Food. 2019;44(1):118–130.
29. Çelik AD, Sarıoğlu T, Dağıstan E. Determination of consumers' attitudes and behaviors towards probiotic products: TR63 Region-Hatay, Kahramanmaraş, Osmaniye provinces example. Mustafa Kemal University Journal of Agricultural Sciences. 2022;27(2):278–287.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Relationship Between Health Fatalism and Self-Care Agency in Oncology Patients

Onkoloji Hastalarında Sağlık Kaderciliği ile Öz Bakım Gücü Arasındaki Ilişki

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ABSTRACT

Aim: *The present study examined the relationship between health fatalism and the self-care agency of oncology patients.*

Material and Methods: *This is a descriptive-correlational study. The study sample consisted of 169 oncology patients who met the inclusion criteria between September 2019, February 2020, and November 2020. The study's data were collected using the Patient Information Form, Health Fatalism Scale, and Self-Care Agency Scale.*

Results: *The patients' mean health fatalism score was 58.62±7.03, and the mean self-care agency score was 87.16±15.52. The difference between the mean scores of health fatalism according to gender, marital status, occupation, income level, and smoking was statistically significant (p<0.05). The difference between the mean self-care scores according to age, education level, smoking, type of treatment, side effects of chemotherapy, and additional chronic disease status was statistically significant (p<0.05). A statistically significant, positive, and low-level relationship was determined between the mean scores of health fatalism and self-care agency (p<0.05).*

Conclusions: *Oncology patients' health fatalism attitudes were found to be high, and their self-care agency was at a moderate level. It was concluded that as the health fatalism attitudes of oncology patients increased, their self-care agency also increased. It is recommended to evaluate the impact of health fatalism as a sociocultural factor in the self-care of oncology patients.*

Key words: *nursing; cancer; self-care; health fatalism*

ÖZET

Amaç: *Bu çalışmanın amacı, onkoloji hastalarının sağlık kaderciliği ile öz bakım gücü arasındaki ilişkiyi incelemektir.*

Gereç ve Yöntem: *Bu araştırma tanımlayıcı-ilişki arayıcı türdedir. Araştırmanın örneklemini, Eylül 2019- Şubat 2020 tarihleri arasında ve Kasım 2020 tarihinde dâhil edilme kriterlerini karşılayan 169 onkoloji hastası oluşturmaktadır. Çalışmanın verileri Hasta Bilgi Formu, Sağlık Kaderciliği Ölçeği ve Öz Bakım Gücü Ölçeği kullanılarak toplandı.*

Bulgular: *Hastaların sağlık kaderciliği puan ortalaması 58,62±7,03 ve öz bakım gücü puan ortalaması 87,16±15,52'dir. Cinsiyet, medeni durum, meslek, gelir düzeyi ve sigara kullanma durumuna göre sağlık kaderciliği puan ortalamaları arasındaki fark istatistiksel olarak anlamlıdır (p<0,05). Yaş, eğitim düzeyi, sigara kullanımı, tedavi türü, kemoterapiye bağlı yaşanan yan etki ve ek kronik hastalık durumuna göre öz bakım gücü puan ortalamaları arasındaki fark istatistiksel olarak anlamlıdır (p<0,05). Hastaların sağlık kaderciliği ile öz bakım gücü puan ortalamaları arasında istatistiksel olarak anlamlı, pozitif ve düşük düzeyde bir ilişki belirlendi (p<0,05).*

Sonuç: *Onkoloji hastalarının sağlık kaderciliği tutumlarının yüksek, öz bakım güçlerinin ise orta düzeyde olduğu bulundu. Onkoloji hastalarının sağlık kaderciliği tutumları arttıkça, öz bakım güçlerinin de arttığı sonucuna varıldı. Onkoloji hastalarının öz bakımında sosyokültürel bir faktör olarak sağlık kaderciliğinin etkisinin değerlendirilmesi önerilebilir.*

Anahtar kelimeler: *hemşirelik; kanser; öz bakım; sağlık kaderciliği*

Introduction

As a chronic disease characterized by uncontrolled cell growth and proliferation, cancer threatens life and affects individuals as a whole with its physical, psychological, social, and economic dimensions[1]. Cancer patients face many problems because of the disease process and the side effects of chemotherapy[2,3]. Cancer experience is a physically and emotionally traumatic process for the individual and may cause regression in self-care agency[4,5]. Cancer patients use self-care

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behaviors such as social support, symptom improvement, drug use, accessing information, using creative activities, and fatigue management[6]. In cancer patients, self-care has the potential to prevent physical and psychosocial problems caused by a cancer diagnosis and chemotherapy treatment and thus improve quality of life[7]. Maintaining self-care continuity is crucial in managing chemotherapy-related symptoms[8].

Nurses should use cultural characteristics such as encouraging individuals to take more responsibility in self-care, coping with the disease, religious beliefs, and socioeconomic levels[9]. Emphasizes the influence of cultural and ethnic factors, such as values and beliefs, in an individual's decisions about prevention, health risk assessment, and treatment[10]. In this context, one of the concepts that affect the health behaviors and outcomes of cancer patients is health fatalism, which generally refers to the belief that health problems are beyond human reach[5]. Health fatalism also emerges as a sociocultural factor and as the belief that health and disease are predetermined and beyond the control of the individual[10].

Cancer fatalism is the attitude that being a cancer patient is beyond one's control and the belief that death is inevitable in the presence of cancer[11,12]. The characteristics of fatalistic attitudes toward cancer include helplessness, pessimism, powerlessness, and the belief that almost everything causes cancer[13]. Patients who have a fatalistic attitude may, therefore, avoid seeking information, healthy behaviors, or cancer screening[14]. Previous studies reported that cancer fatalism is associated with lower participation in cancer screenings,[15,16] avoidance of medical care, and less adherence to cancer prevention behaviors such as exercising, not smoking, and eating fruits and vegetables[17]. Individuals who think that they have cancer by God's will may similarly believe that cancer is unpreventable and incurable[18,19]. If patients have fatalistic solid beliefs about cancer, they may want to avoid a cancer diagnosis or be reluctant to follow recommended treatments[18]. Fatalism may affect self-care activities because it implies that it is impossible to interfere with the destiny that existed outside the person's control long ago and that one cannot go beyond this by making an effort[20].

Religious and sociocultural beliefs are essential in attitudes and behaviors toward health, diagnosis, treatment, and care[21]. Religious beliefs positively and negatively affect health. In a previous study conducted on patients with diabetes, a significant relationship was detected between religious orientation and self-care[22]. It was found that social support and positive thinking increased as fatalism and fighting spirit increased in patients receiving chemotherapy[1]. On the other hand, it has been reported that health fatalism negatively affects the health behaviors of individuals and prevents their active participation in the diagnosis and treatment process[23]. At the same time, patients try to cope with life-threatening situations with their religious tendencies and beliefs, such as praying, especially in the presence of chronic diseases[24,25]. However, studies conducted on patients' spiritual or religious resources, such as fatalism in coping with chronic and critical diseases, are limited in number. The nurse needs to determine whether there is a positive impact of health fatalism in the self-care of the individual with cancer or whether fatalism is an obstacle in self-care. For this reason, the study aimed to examine the relationship between health fatalism and self-care in oncology patients.

Research Questions

- What is the level of health fatalism of oncology patients?
- What is the self-care agency of oncology patients?
- What factors affect oncology patients' health fatalism and self-care agency?
- Is there a relationship between health fatalism and the self-care agency of oncology patients?

Material and Methods

Type of Study

The study had a descriptive-correlational design.

Population and Sample of Study

The study population consisted of oncology patients receiving chemotherapy in the medical oncology clinics of a university research hospital in the east of Türkiye. The sample consisted of 169 oncology patients who met the inclusion criteria between September 2019, February 2020, and November 2020.

The Post-Hoc Power Analysis was used to determine the study's sample size adequacy. The power analysis determined that the study's power was 0.99 at a significance level of 0.05 and 95% Confidence Interval (Correlation H_1=0.525, lower critical r=-0.296, Upper Critical r=0.296, power 0.99). This value shows that the sample is sufficient.

Inclusion Criteria of the Study

- Being 18 years or older
- Receiving chemotherapy treatment
- Absence of any communication problems
- The ability to understand and speak Turkish.

Data Collection Tools

The study data were collected using the "Patient Information Form," "Health Fatalism Scale," and "Self-Care Agency Scale."

The Patient Information Form

The Patient Information Form included questions about the patients' descriptive characteristics (age, gender, educational level, marital status, occupation, income level perception, smoking, and participation in cancer screenings) and questions about disease characteristics (duration of diagnosis, type of cancer, metastasis, treatment type, side effect of chemotherapy, way of perceiving the disease and having an additional chronic disease).

Health Fatalism Scale

The "Health Fatalism Scale" was developed by Franklin, Schlundt, and Wallston[26] in 2008. Bobov and Çapik conducted the Turkish validity and reliability study[27]. The scale has a 5-point Likert design. The Turkish version of the scale has 17 items and is one-dimensional. The factor loads of the items are between 0.47–0.77, and the Cronbach Alpha Coefficient of the scale is 0.91. The scores obtained from the scale are between 17–85, and an increase in the score indicates an increased attitude toward health fatalism[27]. The Cronbach Alpha Coefficient was calculated as 0.83.

Self-Care Agency Scale

Kearney and Fleischer developed the "Self-Care Agency Scale," which has 43 items and determines individuals' interest in self-care actions[28]. It was adapted into Turkish society by Nahcivan[29]. The scale has a 5-point Likert design with 35 items scored between 1–5. Items 3, 6, 9, 13, 19, 22, 26, and 31 are reverse scored. A score between 35 and 140 can be obtained from the scale. An increase in the scale score indicates an increased self-care agency[29]. The Cronbach Alpha Coefficient was calculated as 0.91.

Data Collection

The data were collected through face-to-face interviews with the patients, in cooperation with the oncology clinic team, in a way that there was no follow-up and treatment during the appointed interview hours and that the interviews did not coincide with the patients' meals, sleep, and visiting hours. The patients were informed about the study before the data collection. An informed consent form was presented to the patients at the time of enrollment in the study. The principle of volunteering was taken as the basis by informing that the volunteers were recruited for the study and that the patients could withdraw at any time. For the patients to respond comfortably, the data collection forms were asked of them individually by being alone with the patient, and their preferred options were marked. The data collection took approximately 15 minutes for each oncology patient.

Statistical Analysis

The data analysis was made by using the IBM Statistical Package for Social Sciences (SPSS) version 22 package program. Percentages, numbers, mean, and standard deviation were used in the descriptive analysis of the data. It was found that the Health Fatalism Scale scores were not normally distributed, and the Self-Care Agency Scale scores were normally distributed. In comparing the paired groups, the T-test was used for normally distributed measurements in independent groups, and the Mann-Whitney U-test was used for non-normally distributed measurements. In comparing multiple groups, the Analysis of Variance was used for normally distributed measurements, and the Kruskal-Wallis Analysis was used for non-normally distributed measurements. The Spearman Correlation Analysis was performed to examine the inter-scale relationship. The internal validity of the scales was evaluated with the Cronbach α Coefficient.

Ethics Principles of the Study

The Atatürk University Faculty of Medicine Clinical Research Ethics Committee approved the study (22.04.2019:03/26), and institutional permission was obtained from the Atatürk University Research Hospital, where it was conducted.

Results

This section presents the study's findings, which examined the relationship between health fatalism and self-care in oncology patients. It found that 52.1% of the patients were female, 40.8% were between the ages of 51 and 65, 36.7% were literate, and 90.5% were married. Also, 50.3% of the patients were homemakers, 73.4% had an income equal to their expenses, 82.8% did not smoke, and 94.7% did not participate in cancer screenings (Table 2).

It was also determined that 38.5% of the patients had esophageal stomach cancer, 89.9% had a diagnosis time of 0.1–4 years, 56.2% metastasized, 73.4% received only chemotherapy treatment, 53.8% had nausea and vomiting, 7.7% thought that cancer was an incurable disease, 60.4% thought that there was not much to be done to beat cancer, and 60.4% had no other additional chronic disease (Table 3).

The mean score of the patients' Health Fatalism Scale was 58.62±7.03, and the mean Self-Care Agency Scale score was 87.16±15.52 (Table 1).

The mean score of health fatalism was found to be higher in males, singles, smokers, retirees, and those with less income than expenditure at a statistically significant level

Table 1. *Health Fatalism Scale and Self-Care Agency Scale mean scores*

	Min-max can be obtained	$\bar{X}$±SD
Health Fatalism Scale	17–75	58.62±7.03
Self-Care Agency Scale	44–128	87.16±15.52

Table 2. *Comparison of the sociodemographic features with mean scores of Health Fatalism Scale and Self-Care Agency Scale*

				Health Fatalism Scale	Self-Care Agency Scale
		n	%	$\bar{X}$±SD	$\bar{X}$±SD
Age	30–50	39	23.1	59.28±5.70	92.38±15.42
	51–65	69	40.8	57.20±7.96	87.69±15.93
	66 and above	61	36.1	59.81±6.47	83.22±14.22
	Test, p			KW: 3.299 p: 0.192	F=4.376 p: 0.014
Gender	Female	88	52.1	57.19±8.04	86.11±15.08
	Male	81	47.9	60.18±5.36	88.30±15.99
	Test, p			MWU: 2850p: 0.024	t=-0.918 p: 0.360
Educational level	Illiterate	48	28.4	57.79±5.53	82.58±14.76
	Literate	62	36.7	59.20±6.84	86.12±16.50
	Primary-secondary	48	28.4	58.50±8.43	90.58±13.98
	High school	11	6.5	59.54±7.78	98.09±12.09
	Test, p			KW: 4.043 p: 0.257	F=4.321 p: 0.006
Marital status	Married	153	90.5	58.30±7.24	87.48±15.59
	Single	16	9.5	61.68±3.30	84.12±14.97
	Test, p			MWU: 815.5 p: 0.028	t=0.823 p: 0.412
Occupation	Housewife	85	50.3	57.48±7.86	85.72±15.15
	Self-employment	29	17.2	60.10±4.81	91.41±15.96
	Retired	38	22.5	61.02±5.94	89.60±14.45
	Employee	17	10.1	56.47±6.52	81.64±17.44
	Test, p			KW=9.046 p: 0.029	F=2.033 p: 0.111
Income level perception	Less than income	41	24.3	60.80±6.28	89.12±13.24
	Income is equivalent to expenses	124	73.4	58.30±6.15	86.39±16.19
	More than income	4	2.4	46.25±20.36	91.00±17.26
	Test, p			KW=8.041 p: 0.018	F=0.598 p: 0.551
Smoking	Yes	29	17.2	62.37±4.88	92.24±10.23
	No	140	82.8	57.85±7.17	86.11±16.23
	Test, p			MWU=1246 p: 0.001	t=2.613 p: 0.011
Participating in cancer screenings	Yes	9	5.3	54.33±14.55	89.22±17.83
	No	160	94.7	58.86±6.36	87.05±15.43
	Test, p			MWU=647.5 p: 0.611	t=-0.408 p: 0.684

(p<0.05) (Table 2). Also, the mean score of health fatalism of the patients who disagreed with the statements "*Cancer is an incurable disease*" and "*There is not much I can do to beat cancer*" was found to be higher at a statistically significant level (p<0.05) (Table 3).

It was also found that the mean self-care agency score of patients aged 30–50, high school graduates, and smokers was significantly higher (p<0.05) (Table 2). The difference between the mean self-care agency scores of the patients according to treatment type was statistically significant (p<0.05). In further analysis, the mean self-care agency score of those who received all three treatments was significantly higher than those who responded to chemotherapy, chemotreatment+radiotherapy, and

Table 3. *Comparison of the disease characteristics with mean scores of Health Fatalism Scale and Self-Care Agency Scale*

				Health Fatalism Scale	Self-Care Agency Scale
		n	%	$\bar{X}$±SD	$\bar{X}$±SD
Diagnosis time	0.1–4 years	152	89.9	58.92±6.25	86.46±15.58
	5–9 years	17	10.1	55.94±11.92	93.47±13.83
	Test, p			MWU=1221 p: 0.710	t=-1.777 p: 0.077
Cancer type	Colorectal	17	10.1	57.00±7.09	89.05±17.76
	Breast	12	7.1	55.16±6.63	82.00±12.91
	Lung	22	13.0	58.54±5.67	85.81±18.00
	Esophagus, stomach	65	38.5	60.40±5.67	89.07±15.10
	Pancreas, gall bladder, liver	20	11.8	56.80±11.61	88.10±13.10
	Hematological	6	3.6	54.66±9.15	79.16±24.86
	Genitourinary	15	8.9	57.60±4.23	86.46±11.72
	Other (unknown primary)	12	7.1	61.25±6.03	85.08±15.91
	Test, p			KW=14.09 p: 0.050	F=0.654 p: 0.710
Metastasis	Var	95	56.2	58.53±5.37	85.51±15.88
	Yok	74	43.8	58.74±8.75	89.28±14.87
	Test, p			MWU=3135 p: 0.228	t=-1.573 p: 0.118
Treatment type	Chemotherapy	124	73.4	58.96±7.38	87.70±15.49
	Chemotherapy + radiotherapy	21	12.4	57.57±5.97	79.14±17.17
	Chemotherapy + surgery	15	8.9	56.66±6.52	86.40±11.23
	All three of them	9	5.3	59.66±4.89	99.66±7.59
	Test, p			KW=2.981 p: 0.395	F=4.094 p: 0.008
Side effects of chemotherapy	Nausea-vomiting	91	53.8	59.02±5.62	89.63±14.93
	Constipation	6	3.6	56.66±2.33	76.00±11.17
	Diarrhea	10	5.9	60.30±4.90	89.10±15.77
	Abdomen pain	10	5.9	54.80±15.00	85.10±19.26
	Fatigue	32	18.9	58.93±6.45	84.50±16.27
	Dyspnea	7	4.1	55.57±6.10	71.42±9.71
	Loss of appetite	13	4.2	59.30±10.76	90.15±12.80
	Test, p			KW=6.146 p: 0.407	F=2.525 p: 0.023
Cancer is an incurable disease.	I agree	13	7.7	55.15±6.26	74.38±19.11
	I do not agree	156	92.3	58.91±7.03	88.23±14.76
	Test, p			MWU=643.5 p: 0.029	t=-3.173 p: 0.002
There is not much I can do to beat cancer.	I agree	102	60.4	57.97±5.86	83.61±16.10
	I do not agree	67	39.6	59.62±8.45	92.56±12.92
	Test, p			MWU=2679 p: 0.018	t=-2.802 p: 0.006
Additional chronic disease	Yes	67	39.6	59.04±6.37	83.11±15.46
	No	102	60.4	58.35±7.45	89.82±15.04
	Test, p			MWU=3363 p: 0.863	t=-2.802 p: 0.006

Table 4. *The relationship between Health Fatalism Scale and Self-Care Agency Scale*

		Self-Care Agency Scale
Health Fatalism Scale	r	0.274
	p	0.000

chemotherapy+surgery. On the other hand, it was determined that the self-care agency of the patients who had dyspnea and had additional chronic diseases was significantly lower ($p<0.05$). The self-care agency of the patients who disagreed with the statements "*Cancer is an incurable disease*" and "*There is not much I can do to beat cancer*" was found to be higher at a statistically significant level ($p<0.05$) (Table 3).

A statistically significant, positive, and low-level relationship was detected between the Health Fatalism Scale and the Self-Care Agency Scale mean scores ($r=0.274$ $p<0.01$) (Table 4).

Discussion

In the present study, in which the relationship between health fatalism and self-care agency of oncology patients was investigated, it was found that the patients' health fatalism attitudes were high. In a study conducted on breast cancer, it was reported that women who had mammography had lower health fatalism scores[30]. In another study conducted with individuals diagnosed with breast cancer, cancer fatalism was found to be low[31]. In another study, it was reported that the majority of the participants did not agree with the opinion that "*There is not much you can do to reduce your chance of having cancer.*" In contrast, more than half of them agreed with the opinion that "*When I think about cancer, I automatically think of death.*"[14] In another study, it was determined that most of the patients with advanced lung and bowel cancer believe that "*Cancer is curable.*"[32] The high health fatalism score in this study may be because of the sociocultural characteristics of the region.

It was determined in the study that the self-care agency of oncology patients was at a moderate level. Although the mean score of self-care agency was found to be high in patients with gynecological cancer,[33] was found to be moderate in patients who underwent surgery for head and neck cancer[34]. O'Regan et al.[6] reported high self-care agency in patients with breast, colorectal, Hodgkin, and non-Hodgkin lymphoma cancer patients receiving chemotherapy[6]. Self-care and self-efficacy scores were moderate in Chinese gastric and colorectal cancer patients[35]. In another study on breast cancer patients receiving chemotherapy in China, the self-care agency score was moderate[36]. In this study, it can be considered that the self-care agency was at a moderate level because of the chemotherapy-related symptoms, additional chronic diseases, or the majority of patients' age was 51 and over.

As a result of this study, the mean score of health fatalism score of men was found to be significantly higher than that of women. In a literature review on cancer fatalism, it was determined that women had higher fatalism scores[13]. In the study of Kaya and Bozkur[20] and Bobov and Çapik[27], fatalism tendency was higher in women. Because of the patriarchal structure of Turkish society, men may perceive the disease as an adverse condition affecting their level of competence. For this reason, it can be considered that men preferred fatalism as a coping method in this study.

In the present study, the health fatalism score of singles was found to be higher than that of married people. In the studies of Bobov and Çapik, married people had higher fatalism scores[27]. The reason why singles' health fatalism score was high in this study may be that single people attributed their disease more to fate or divine intervention or that the rate of singles was low in the study.

It was determined that retirees' mean health fatalism score was higher than homemakers and workers. In the study of Bobov and Çapik, homemakers were found to have higher fatalism scores[27]. In one study, it was determined that unemployed, retired, and non-working individuals had higher fatalism scores than other occupational groups[23]. This study suggests that retired individuals may have a fatalistic tendency to surrender after a long working period.

Health fatalism scores of patients whose income was less than their expenses were found to be higher. Studies are reporting that individuals who have low income have higher fatalism scores [19,23,27,37]. Michielutte et al. found that only a few patients showed a fatalistic approach in a sample with a high annual income[38]. On the other hand, other studies did not find a relationship between economic status and cancer fatalism[25]. Low-income individuals may associate their problems with a more fatalistic approach for economic reasons,

or they may turn to the health fatalism approach because of their inability to access information sources.

In this study, smokers were found to have higher health fatalism scores. One study found that smoking and being less ready to quit were associated with fatalistic beliefs[39]. In a study, it was reported that smokers had higher fatalism levels, and patients believed that they had cancer because they should have cancer[40]. In another study, it was reported that people with fatalistic beliefs about preventing cancer had reduced smoking avoidance behavior[41]. According to the results of this study, it can be considered that individuals with high health fatalism have a higher probability of smoking, which will negatively affect the fight against cancer.

The health fatalism score of those who agreed with the statements "*Cancer is an incurable disease*" and "*There is not much I can do to beat cancer*" was found to be significantly lower than those who did not, in the study of Duberstein et al. stated that most patients believed cancer could be cured[32]. In a previous study, it was reported that nearly half of the patients who had breast cancer agreed with the statement, "*I believe that it is part of God's plan for someone to have breast cancer*"[31]. In this study, it can be considered that those who agreed with the statement "*Cancer is an incurable disease*" and "*There is not much I can do to beat cancer*" were less likely to have health fatalism because of the knowledge that patients gained about the treatment after the cancer diagnosis or the positive effect of religious beliefs on this perception.

The self-care agency of individuals aged 30–50 was higher in the study. The self-care agency of patients who underwent surgery for head and neck cancer did not show a significant difference according to age[34]. No relationship between age and infection prevention self-care behaviors in hematology cancer patients was detected[42]. In parallel with this study, studies report that self-care agency decreases as age increases in cancer patients[35,43]. There might be a decrease in self-care agencies with the increase in possible health problems and the presence of more physical disabilities in advanced ages.

This study also determined that the self-care agency of high school graduate patients was significantly higher. Similar to this study, a positive correlation was reported between training and self-care agency in studies conducted on lung cancer patients,[44] head and neck cancer patients,[34] and gastric colorectal cancer patients[35]. Patients may search for more information about self-care skills with the increased training levels. Individuals' self-care agency might be positively affected by increased awareness of diseases.

It was found that smokers had higher self-care agency. In a previous study, it was reported that smoking cancer patients had lower self-care agency than non-smokers[43]. This study suggests that patients who have high self-care agency may be less sensitive to quitting smoking after their diagnosis. Also, this study's lower number of smokers might have affected this result.

In this study, the self-care agency of patients who received chemotherapy, radiotherapy, and surgical treatment was significantly higher. In one study, a difference was found in the self-care agency of breast cancer patients who received only chemotherapy and patients who received chemotherapy+radiotherapy [36]. In this study, the difference in self-care agency according to the type of treatment may be due to the physical functionality of patients receiving all three treatments. It was determined in this study that dyspnea decreased the self-care agency of patients more than chemotherapy side effects such as nausea-vomiting, diarrhea, fatigue, and loss of appetite. A previous study reported that cancer patients have difficulty managing daily tasks related to chemotherapy, which affects their health-related quality of life.[4] Patients with dyspnea might have trouble managing their daily activities, and therefore, their self-care agency might have decreased in this study. It was also determined that additional chronic disease reduces the self-care agency of the patients. Another study found that past medical history did not affect self-care in Iranian cancer patients[43]. It was determined that there was no relationship between comorbidity and self-care agency in breast cancer patients[36] and gastric colorectal cancer patients[35]. In this study, the possibility of those who had other chronic diseases having more problems coping with the effects of cancer might have reduced their self-care agency.

In the present study, the self-care agency of the patients who did not agree with the statements "*Cancer is an incurable disease*" and "*There is not much I can do to beat cancer*" was found to be significantly higher than those who agreed with these statements. It can be considered that patients who believe in the curability of cancer and are aware of what they can do to beat cancer have higher self-care agency because they can be more motivated. This finding may indicate that adequate information about the treatment and care of cancer is the preliminary strategy for self-care.

It was found that as the patients' health fatalism approach increased, their self-care agency scores also increased. In a qualitative study conducted with diabetes patients, the three main themes that explained self-care were fatalism, belief in God, and fear of complications, and it was also found that these themes supported self-care[45]. In another study that was conducted with diabetic patients, it was found that diabetes fatalism was negatively associated with drug compliance, exercise, diet, and blood glucose tests[46]. A fatalistic approach can affect health-related activities positively or negatively because of its association with a spiritual force. It was determined in a study conducted with prostate cancer patients that the bond established with God is an essential factor in emotional and social functionality[47]. It is reported that cancer patients who rely on spiritual and religious beliefs accept their disease and try to cope with the disease positively and purposefully[48]. In a study conducted on women who had breast cancer, fatalism, which is one of the ways of coping with cancer, was evaluated as an active confrontation with the disease[49]. It was found that as fatalism increased in patients who received chemotherapy, social support and positive thinking also increased[1]. However, fatalism can be an adaptive response in situations such as waiting for test results related to a diagnosis[1]. Based on a positive point of view, fatalism is considered to increase the self-care agency of patients by reframing a stressful situation positively, providing active acceptance of the disease without submission, and because of the influence of religious beliefs.

Implications for Practice and Future Research

As a result of the present study, it was concluded that as health fatalism increases in cancer patients, self-care agency also increases. As a result of this study, it can be suggested that sociocultural beliefs such as health fatalism should be evaluated as a part of care and rehabilitation. It is also recommended that the positive effect of the health fatalism approach on self-care agency should be integrated into nursing care. In addition, the negative impact of health fatalism on non-smoking health behavior should be eliminated. In the future, studies can be conducted to investigate the relationship between health fatalism and religious coping resources in increasing the self-care agency of the individual or dealing with cancer according to cancer type.

Strengths and Limitations of the Study

Fatalism and religious experiences may differ significantly between countries with different spiritual traditions. This study reveals the effects of health fatalism on self-care in Turkish culture. The study's limitations were that the data were collected in a single hospital and 169 patients, and no comparisons were made with other institutions. The limitation of this study is that it used a self-report questionnaire to assess self-care agency; the self-report questionnaire method has the disadvantage of eliciting only socially acceptable responses, and hence, it may overestimate the level of self-care agency. However, self-reported measures are simple and economical to use.

Conclusion

As a result of the present study, it was found that the health fatalism attitude of cancer patients was high, and their self-care agency was at a moderate level. Health fatalism was found to be higher among men, singles, retirees, low-income participants, and smokers. According to these results, preventing the negative effect of health fatalism on health behaviors is essential. Also, those who were in the 30–50 age range, high school graduates, and smokers had high self-care agency scores, and those with respiratory distress and additional chronic diseases had low scores. Nurses need to consider the factors affecting oncology patients' self-care agency. On the other hand, it was also found that the patients who did not agree with the fatalistic statements about cancer, such as "Cancer is an incurable disease" and "There is not much I can do to beat cancer," had higher health fatalism and self-care agency scores than those who agreed with these statements. This result may show that high health fatalism does not cause fatalistic beliefs in cancer. It was found in the study that the lack of cancer fatalism provided positive support for self-care. In the study, it was concluded that as health fatalism increases in cancer patients, self-care agency also increases. The positive effect of health fatalism in increasing self-care agency is recommended to be integrated into patients' self-care.

Ethical Approval

This study was received on 22/04/2019, meeting number 3 / Decision number 26. Approval was taken from Atatürk University Faculty of Medicine Clinical Research Ethics Committee.

Conflict of Interests

The authors declared no conflict of interest.

Author Contributions

Concept– MŞG; Design– MŞG; Data Collection and/or Processing– MŞG, SG; Analysis and/or Interpretation– MŞG, SG; Resources– MŞG, SG; Literature Search– MŞG, SG; Supervision– MŞG; Writing Manuscript– MŞG, SG; Critical Review– MŞG.

References

1. Lauriola M, Tomai M. Biopsychosocial correlates of adjustment to cancer during chemotherapy: the key role of health-related quality of life. The Scientific World Journal, 2019, 2019.
2. Hintistan S, Çilingir D, Nural N, Gürsoy AA. Hematolojik kanserli hastaların kemoterapiye bağlı yaşadıkları semptomlara yönelik uygulamaları. Gümüşhane Üniversitesi Sağlık Bilimleri Dergisi. 2012;1:153–64.
3. Seven M, Akyüz A, Sever N, Dinçer Ş. Kanser Tanısı Alan Hastaların Yaşadığı Fiziksel ve Psikolojik Semptomların Belirlenmesi. TAF Preventive Medicine Bulletin. 2013;12.
4. Wagland R, Richardson A, Ewings S, Armes J, Lennan E, Hankins M, et al. Prevalence of cancer chemotherapy-related problems, their relation to health-related quality of life and associated supportive care: a cross-sectional survey. Supportive Care in Cancer. 2016;24:4901–11.
5. Nageeb S, Vu M, Malik S, Quinn MT, Cursio J, Padela AI. Adapting a religious health fatalism measure for use in Muslim populations. Plos One. 2018;13:e0206898.
6. O'Regan P, McCarthy G, O'Reilly S, Power D, Bird BH, Murphy CG, et al. Cancer-related fatigue and self-care agency: A multicentre survey of patients receiving chemotherapy. Journal of Clinical Nursing. 2019;28:4424–33.
7. Shams S, Jabbar AA, Nanji K, Jan R, Tharani A. Influence of supportive care on chemotherapy patients' self-care behaviour and satisfaction: A pilot study conducted in Karachi, Pakistan. Indian Journal of Cancer. 2018;55:115–21.
8. Karadağlı F, Alpar ŞE. Bir ölçek geliştirme çalışması: Kemoterapi uygulanan hastalarda özbakım yetersizliği kuramına gore özbakım davranışları ölçeği. Mersin Üniversitesi Sağlık Bilimleri Dergisi. 2017;10:168–81.
9. Sungur G. Kültürlerarası Hemşirelik. İçinde: Seviğ Ü TG (editör) . İstanbul, İstanbul Kitabevi. 2012;181–202.
10. Heiniger LE, Sherman KA, Shaw L-KE, Costa D. Fatalism and health promoting behaviors in Chinese and Korean immigrants and Caucasians. Journal of Immigrant and Minority Health. 2015;17:165–71.
11. Keller KG, Toriola AT, Schneider JK. The relationship between cancer fatalism and education. Cancer Causes & Control. 2021;32:109–18.
12. Kulakci H, Ayyildiz TK, Yildirim N, Ozturk O, Topan AK, Tasdemir N. Effects of breast cancer fatalism on breast cancer awareness among nursing students in Turkey. Asian Pacific Journal of Cancer Prevention. 2015;16:3565–72.
13. Powe BD, Finnie R. Cancer fatalism: the state of the science. Cancer Nursing. 2003;26:454–67.
14. Kobayashi LC, Smith SG. Cancer fatalism, literacy, and cancer information seeking in the American public. Health Education & Behavior. 2016;43:461–70.
15. Peek ME, Sayad JV, Markwardt R. Fear, fatalism and breast cancer screening in low-income African-American women: the role of clinicians and the health care system. Journal of General Internal Medicine. 2008;23:1847–53.
16. Liang W, Wang JH, Chen M-Y, Feng S, Lee M, Schwartz MD, et al. Developing and validating a measure of Chinese cultural views of health and cancer. Health Education & Behavior. 2008;35:361–75.
17. Schmidt C. Fatalism may fuel cancer-causing behaviors. 2007.
18. Sinky TH, Faith J, Lindly O, Thorburn S. Cancer fatalism and preferred sources of cancer information: an assessment using 2012 hints data. Journal of Cancer Education. 2018;33:231–7.
19. Abraído-Lanza AF, Martins MC, Shelton RC, Flórez KR. Breast cancer screening among Dominican Latinas: A closer look at fatalism and other social and cultural factors. Health Education & Behavior. 2015;42:633–41.
20. Kaya A, Bozkur B. Kadercilik eğilimi ile özyeterlik inancı ve savunma mekanizmaları arasındaki ilişkinin incelenmesi. Ege Eğitim Dergisi. 2017;18:124–45.
21. Kiyak E, Erkal E, Demir S, Demirkiran BC, Uren Y, Erguney S. Evaluation of attitudes toward epilepsy and health fatalism in northeastern Turkey. Epilepsy & Behavior. 2021;115:107495.
22. Jafari Y, Rahimi J, Bknazar S, Lashkardoost H, Mohaddes HH, Mousavi JS, et al. The relationship between religious orientation and self-care practice in patients with type 2 diabetes. 2015.
23. Franklin MD, Schlundt DG, McClellan LH, Kinebrew T, Sheats J, Belue R, et al. Religious fatalism and its association with health behaviors and outcomes. American Journal of Health Behavior. 2007;31:563–72.
24. Çınar F, Eti Aslan F. Spiritualism and nursing: The importance of spiritual care in intensive care patients. 2017.
25. Bakan AB, Aslan G, Yıldız M. Determination of breast cancer fatalism in women and the investigation of the relationship between women's cervical cancer and pap smear test health beliefs with religious orientation and fatalism. Journal of Religion and Health. 2021;60:1856–76.
26. Franklin MD, Schlundt DG, Wallston KA. Development and validation of a religious health fatalism measure for the African-American faith community. Journal of Health Psychology. 2008;13:323–35.
27. Bobov G, Capik C. The reliability and validity of the religious health fatalism scale in Turkish language. Journal of Religion and Health. 2020;59:1080–95.

28. Kearney BY, Fleischer BJ. Development of an instrument to measure exercise of self-care agency. Research in Nursing & Health. 1979;2:25–34.
29. Nahcivan N. Sağlıklı gençlerde öz-bakım gücü ve aile ortamının etkisi. Sağlık Bilimleri Enstitüsü, Hemşirelik Anabilim Dalı. İstanbul: İstanbul Üniversitesi, 1993.
30. Molaei-Zardanjani M, Savabi-Esfahani M, Taleghani F. Fatalism in breast cancer and performing mammography on women with or without a family history of breast cancer. BMC Women's Health. 2019;19:1–5.
31. Gullatte MM, Brawley O, Kinney A, Powe B, Mooney K. Religiosity, spirituality, and cancer fatalism beliefs on delay in breast cancer diagnosis in African American women. Journal of Religion and Health. 2010;49:62–72.
32. Duberstein PR, Chen M, Chapman BP, Hoerger M, Saeed F, Guancial E, et al. Fatalism and educational disparities in beliefs about the curability of advanced cancer. Patient Education and Counseling. 2018;101:113–8.
33. Küçükkkaya B, Erçel Ö. Jinekolojik kanserli hastalarda hastalik algisinin öz-bakim gücüne etkisi. Ege Üniversitesi Hemşirelik Fakültesi Dergisi. 2019;35:137–45.
34. Üstündağ H, Zengin N. Baş boyun kanseri nedeni ile cerrahi girişim geçiren hastaların öz bakım gücünün değerlendirilmesi. Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi. 2008;11:63–8.
35. Qian H, Yuan C. Factors associated with self-care self-efficacy among gastric and colorectal cancer patients. Cancer Nursing. 2012;35:E22-E31.
36. Zhang Y, Kwekkeboom K, Petrini M. Uncertainty, self-efficacy, and self-care behavior in patients with breast cancer undergoing chemotherapy in China. Cancer Nursing. 2015;38:E19-E26.
37. Leyva B, Nguyen AB, Cuevas A, Taplin SH, Moser RP, Allen JD. Sociodemographic correlates of cancer fatalism and the moderating role of religiosity: Results from a nationally-representative survey. Journal of Prevention & Intervention in the Community. 2020;48:29–46.
38. Michielutte R, Dignan MB, Sharp PC, Boxley J, Wells HB. Skin cancer prevention and early detection practices in a sample of rural women. Preventive Medicine. 1996;25:673–83.
39. Schnoll RA, Malstrom M, James C, Rothman RL, Miller SM, Ridge JA, et al. Correlates of tobacco use among smokers and recent quitters diagnosed with cancer. Patient Education and Counseling. 2002;46:137–45.
40. Hall MB, Vos P. Comparison of cancer fatalism among rural smokers and nonsmokers. Journal of Community Health. 2019;44:215–21.
41. Kim HK, Lwin MO. Cultural determinants of cancer fatalism and cancer prevention behaviors among Asians in Singapore. Health Communication. 2021;36:940–9.
42. Han A, Choi JS. Factors influencing infection prevention self-care behaviors in patients with hematologic cancer after discharge. European Journal of Oncology Nursing. 2018;35:102–6.
43. Goudarzian AH, Boyle C, Beik S, Jafari A, Bagheri Nesami M, Taebi M, et al. Self-care in Iranian cancer patients: The role of religious coping. Journal of Religion and Health, 2019;58:259–270.
44. Altıparmak S, Fadıloğlu Ç, Gürsoy ŞT, Altıparmak O. Kemoterapi tedavisi alan akciğer kanserli hastalarda öz bakım gücü ve yaşam kalitesi ilişkisi. Ege Tıp Dergisi, 2011;50:95–102.
45. Saidi S, Milnes LJ, Griffiths J. Fatalism, faith and fear: A case study of self-care practice among adults with Type 2 diabetes in urban Malaysia. Journal of Clinical Nursing, 2018;27:3758–3767.
46. Walker RJ, Smalls BL, Hernandez-Tejada MA, Campbell JA, Davis KS, Egede LE. Effect of diabetes fatalism on medication adherence and self-care behaviors in adults with diabetes. General Hospital Psychiatry, 2012;34:598–603.
47. Gall TL. Relationship with God and the quality of life of prostate cancer survivors. Quality of Life Research, 2004;13:1357–1368.
48. Weaver AJ, Flannelly KJ. The role of religion/spirituality for cancer patients and their caregivers. Southern Medical Journal, 2004;97:1210–1214.
49. Levine EG, Targ E. Spiritual correlates of functional well-being in women with breast cancer. Integrative Cancer Therapies, 2002;1:166–174.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Bacteria Isolated from Endotracheal Aspirates of Patients in Intensive Care Units: A Single-Centre Retrospective Study

Yoğun Bakım Ünitelerindeki Hastaların Endotrakeal Aspiratlarından İzole Edilen Bakterilerin Değerlendirilmesi: Tek Merkezli Retrospektif Bir Çalışma

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ABSTRACT

Aim: *This study aims to analyze the bacteriological profile and antibiotic susceptibility patterns of isolates from endotracheal aspirates (ETAs) of intensive care units (ICUs) patients to provide data for combating ventilator-associated pneumonia (VAP) and other nosocomial infections.*

Material and Methods: *A retrospective study of ETA (Endotracheal Aspirate) samples from ICU patients (January-December 2022) was conducted. Quantitative cultures were performed on the ETA samples, and the results were expressed as CFU/mL (colony-forming units per milliliter). Bacteria were identified and tested for antibiotic susceptibility according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.*

Results: *Among 263 isolates, predominant gram-negative bacteria were Acinetobacter baumannii, Pseudomonas aeruginosa, and Klebsiella spp., gram-positive bacteria included Staphylococcus epidermidis and Staphylococcus aureus. High resistance was noted in Acinetobacter baumannii to ciprofloxacin (96.4%) and piperacillin/tazobactam (97.3%). Staphylococcus epidermidis showed resistance to oxacillin (66.6%) but none to vancomycin or linezolid.*

Conclusions: *The prevalence of multidrug-resistant pathogens in ETA cultures emphasizes the importance of improved surveillance, antimicrobial stewardship and infection control in ICUs.*

Key words: ventilator-associated *pneumonia; endotracheal aspirates; antibiotic resistance*

ÖZET

Amaç: *Bu çalışmada, ventilatör ile ilişkili pnömoni (VİP) ve diğer hastane enfeksiyonlarıyla mücadele için veri sağlamak amacıyla yoğun bakım ünitelerindeki (YBÜ) hastaların endotrakeal aspiratlarından (ETA) izole edilen suşların bakteriyolojik profili ve antibiyotik duyarlılık paternleri analiz edilmiştir.*

Gereç ve Yöntem: *YBÜ hastalarından alınan ETA örnekleri retrospektif (Ocak-Aralık 2022) olarak değerlendirilmiştir. Endotrakeal aspirat örnekleri üzerinde kantitatif kültürler yapılmış ve sonuçlar CFU/mL (mililitre başına koloni oluşturan birim) olarak ifade edilmiştir. Tanımlanmış olan bakteriler EUCAST (Avrupa Antimikrobiyal Duyarlılık Testi Komitesi) kriterlerine göre antibiyotik duyarlılığı açısından test edilmiştir.*

Bulgular: *263 izolat arasında, en sık saptanan gram-negatif bakteriler Acinetobacter baumannii, Pseudomonas aeruginosa ve Klebsiella spp. iken, gram-pozitif bakteriler Staphylococcus epidermidis ve Staphylococcus aureus idi. Acinetobacter baumannii'de siprofloksasin (%96,4) ve piperasilin-tazobaktama (%97,3) karşı yüksek direnç kaydedilmiştir. Staphylococcus epidermidis suşlarında oksasiline (%66,6) direnç tespit edilmişken vankomisin veya linezolide direnç görülmemiştir.*

Sonuç: *ETA kültürlerinde çoklu ilaca dirençli patojenlerin yüksek oranda tespit edilmesi, YBÜ'lerde gelişmiş sürveyans, antimikrobiyal yönetim ve enfeksiyon kontrolünün önemini vurgulamaktadır.*

Anahtar kelimeler: *ventilatör ilişkili pnömoni; endotrakeal aspirat; antibiyotik direnci*

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Introduction

Ventilator-associated pneumonia (VAP) is a significant hospital-acquired infection, particularly prevalent in intensive care units (ICUs) where patients are dependent on mechanical ventilation. Diagnosing VAP and determining appropriate antibiotic therapy depends on accurately identifying bacterial pathogens and their antibiotic susceptibility patterns from endotracheal aspirate (ETA) cultures. The significance of ETA cultures lies in their ability to provide crucial microbiological data that guide targeted treatment, thereby improving patient outcomes and reducing the incidence of multidrug-resistant infections.

Several studies have highlighted the prevalence and variety of bacterial pathogens isolated from ETAs. Gram-negative bacteria, including *Acinetobacter baumannii* (*A.baumannii*), *Klebsiella pneumoniae* (*K.pneumoniae*), and *Pseudomonas aeruginosa (P.aeruginosa*), are frequently identified as predominant pathogens, often exhibiting multidrug resistance (MDR). Gram-positive bacteria, such as *Staphylococcus aureus* (*S.aureus*), including methicillin-resistant strains (MRSA), are also commonly isolated[1–3].

The management of VAP involves empiric antibiotic therapy, typically starting with broad-spectrum antibiotics and later de-escalating based on culture results. Rapid identification of pathogens and their resistance profiles can significantly reduce the duration of inappropriate antibiotic use, thereby mitigating the development of resistance and improving clinical outcomes[4].

This study aims to comprehensively analyze the bacteriological profile and antibiotic susceptibility patterns of isolates from ETAs in ICU patients at our center, contributing valuable data to the ongoing efforts to combat VAP and other nosocomial infections in critically ill patients.

Material and Methods

The study was approved by the Ethics Committee of Health Sciences University Bursa Yüksek İhtisas Training and Research Hospital (Approval No: 2011-KAEK-25, Date: 2023/06/01). This retrospective study investigated the bacteria isolated from endotracheal aspirate samples of patients admitted to our hospital's Medical and Surgical ICUs between January 2022 and December 2022 and their antibiotic susceptibilities.

Inclusion criteria were hospitalization in the ICU for ≥48 hours and growth of ≥100.000 cfu/ml in endotracheal aspirate cultures. Exclusion criteria were incomplete medical records, polymicrobial growth or contamination in cultures, or age <18 years. Data on patient demographics, microbiological results, and antibiotic susceptibilities were retrieved retrospectively from the hospital's electronic database.

The hospital's microbiology laboratory routinely processed endotracheal aspirate samples. Clinical specimens were inoculated onto 5% sheep blood agar and eosin methylene blue (EMB) agar. Plates were incubated at 37°C for 18–24 hours. Pure cultures with ≥100.000 cfu/ml were identified using conventional biochemical methods. Antibiotic susceptibility testing was performed via disc diffusion and gradient tests (Etest, bioMérieux, France) following European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.

Empirical therapy for gram-negative bacteria included broad-spectrum antibiotics such as piperacillin/tazobactam, meropenem, and ciprofloxacin. For gram-positive bacteria, vancomycin, teicoplanin, and linezolid were preferred.

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS) for Windows program version 28.0. Descriptive statistics (numbers, percentages, means, and standard deviations) were used to summarize the distribution of isolated microorganisms, antibiotic resistance patterns, and patient demographics.

Results

Two hundred and fifteen patients met the inclusion criteria and were enrolled in the study. The cohort included 136 males (63.3%) and 79 females (36.7%), with a mean age of 65.2±12.8 years (range: 18–92). Overall, 263 microorganisms were isolated. Among these, *A.baumannii* was the most frequently isolated microorganism, accounting for 43.0%. *P.aeruginosa*, *Klebsiella spp*., and *Escherichia coli* (*E.coli*) followed this. *Stenotrophomonas maltophilia* (*S.maltophilia)* and *Enterobacter spp*. were less common, representing 0.8% and 1.9%, respectively (Table 1).

Among gram-positive bacteria, *Staphylococcus epidermidis* (*S.epidermidis*) and *S.aureus* were the primary isolates (Table 2). Eleven (4.2%) *Candida spp*. were detected among the isolated microorganisms.

A.baumannii (n=113) exhibited high resistance rates to multiple antibiotics, with the highest resistance observed against ciprofloxacin (96.4%) and

Table 1. *Resistance rates of gram-negative microorganisms to various antibiotics*

Microorganism (n)	Co-trimoxazole n (%)	Ceftazidime-Avibactam n (%)	Ciprofloxacin n (%)	Cefoperazone/ sulbactam n (%)	Piperacillin/ tazobactam n (%)	Meropenem n (%)	Amikacin n (%)
A.baumannii (n=113)	34 (30.0)	-	100 (96.4)	-	-	108 (95.5)	20 (17.6)
P.aeruginosa (n=34)	32 (94.1)	1 (2.9)	9 (26.4)	11 (32.3)	11 (32.3)	5 (14.7)	4 (11.7)
Klebsiella spp. (n=33)	29 (87.8)	2 (6.0)	28 (84.8)	29 (87.8)	29 (87.8)	11 (33.3)	7 (21.2)
E.coli (n=46)	11 (23.9)	0 (0)	20 (43.4)	11 (23.9)	10 (21.7)	11 (23.9)	7 (15.2)
S.maltophilia (n=2)	0 (0)	-	-	-	-	-	-
Enterobacter spp. (n=5)	0 (0)	0 (0)	2 (40.0)	1 (20.0)	2 (40.0)	1 (20.0)	1 (20.0)

Table 2. *Resistance rates of gram-positive microorganisms to various antibiotics*

Microorganism (n)	Oxacillin n (%)	Vancomycin n (%)	Teicoplanin n (%)	Linezolid n (%)	Ciprofloxacin n (%)
S.epidermidis (n=12)	8 (66.7)	0 (0)	0 (0)	0 (0)	5 (41.7)
S.aureus (n=7)	5 (71.4)	0 (0)	0 (0)	0 (0)	6 (85.7)

Table 3. *Antibiotic regimens administered to the microorganisms grown in endotracheal aspirate cultures that were considered to be VAP agents*

Treatment	*A.baumannii* (n=86)	*P.aeruginosa* (n=34)	*Klebsiella spp.* (n=28)	*E.coli* (n=41)	*S.maltophilia* (n=2)	*Enterobacter spp.* (n=5)	*S.epidermidis* (n=3)	*S.aureus* (n=6)
Monotherapy, n (%)	5 (5.8)	31 (91.2)	24 (85.7)	33 (80.5)	2 (100)	3 (60.0)	3 (100)	6 (100)
Meropenem, n (%)	-	22 (64.7)	13 (46.4)	23 (56.1)	-	3 (60.0)	-	-
Colistin, n (%)	5 (5.8)	-	-	-	-	-	-	-
Tigecycline, n (%)	-	-	4 (14.3)	-	-	-	-	-
Vancomycin, n (%)	-	-	-	-	-	-	1 (33.3)	4 (66.7)
Linezolid, n (%)	-						2 (66.7)	2 (33.3)
Co-trimoxazole, n (%)	-	-	-	-	2 (100)	-	-	-
Piperacillin/tazobactam, n (%)	-	9 (26.5)	2 (7.1)	9 (22.0)	-	-	-	-
Ceftazidime/avibactam, n (%)	-	-	5 (17.9)	1 (2.4)	-	-	-	-
Combination therapy, n (%)	81 (94.2)	3 (8.8)	4 (14.3)	8 (19.5)	0 (0)	2 (40.0)	0 (0)	0 (0)
Meropenem + Colistin, n (%)	4 (4.6)	1 (2.9)	4 (14.3)	-	-	2 (40.0)	-	-
Meropenem + Tigesiklin, n (%)	11 (12.7)	-	-	3 (7.3)	-	-	-	-
Sefaperazon/sulbaktam + Colistin, n (%)	49 (56.9)	-	-	-	-	-	-	-
Meropenem + Amikasin, n (%)	17 (19.7)	-	-	-	-	-	-	-
Piperacillin/tazobactam + Amikacin, n (%)	-	2 (5.9)	-	5 (12.2)	-	-	-	-

meropenem (95.5%). *P.aeruginosa* (n=34) showed notable resistance to cotrimoxazole (94.1%) and ciprofloxacin (26.4%), while resistance to colistin was 11.7%. *Klebsiella spp.* (n=33) had high resistance rates to multiple antibiotics, including ciprofloxacin (84.8%), cotrimoxazole (87.8%), and piperacillin/tazobactam (87.8%). *E.coli* (n=46) exhibited the highest resistance to ciprofloxacin (43.4%) and relatively lower resistance to other antibiotics. *S.maltophilia* (n=2) isolates were susceptible to co-timoxazole. *Enterobacter spp*. (n=5) isolates showed the highest resistance rates to ciprofloxacin and piperacillin/tazobactam (Table 3).

Among gram-positive bacteria, *S.epidermidis* (n=12) demonstrated a high resistance rate to oxacillin (66.6%), and ciprofloxacin (41.6%), but no resistance was observed for vancomycin,

teicoplanin, and linezolid. *S.aureus* (n=7) isolates showed a high resistance rate to oxacillin (71.4%) and ciprofloxacin (85.7%), while no resistance was detected for vancomycin, teicoplanin, and linezolid (Table 2).

Discussion

Ventilator-associated pneumonia is a severe infectious disease affected by various factors, such as the patient population in intensive care units, the length of hospital stay, and previous antimicrobial treatment[5]. It is commonly caused by microorganisms such as *P.aeruginosa*, *S.aureus*, *A.baumannii*, and *Klebsiella pneumoniae (K.pneumoniae)* in intensive care units[6,7].

In our study, gram-negative bacteria were dominant among the strains isolated from ETA samples of ICU patients. These pathogens are frequently associated with healthcare-associated infections and are usually multidrug resistant, which makes treatment difficult[4,8]. Among the gram-negative bacteria identified in our study, the high resistance rates observed in *A.baumannii*, *Klebsiella spp*., and *P.aeruginosa* are consistent with reports from other regions and underline the global challenge posed by these MDR organisms. In a study investigating the microorganisms causing VAP in Türkiye, gram-negative organisms were found in 76.5% of cases[9]. In another study conducted in Türkiye, *A.baumannii* and *P.aeruginosa* were found in 49.5% and 20.5% of ETA samples, respectively[10]. In another study conducted in India, Pseudomonas Spp. (18%), Escherichia coli (25%) and Klebsiella pneumonia (36%) were identified as the common pathogens causing VAP[11]. In our study, gram-negative microorganisms were found in 88.6% of the cases, and the most frequently grown agent was *A.baumannii*, which had a remarkable rate.

Our study identified *A.baumannii* strains as the agent with the highest degree of resistance. In a study conducted in Türkiye in which VAP agents were evaluated, ciprofloxacin resistance was found in 63.6% of *A.baumannii*. In another study conducted in our country, the meropenem resistance rate was 90% in *A.baumannii*[8,12]. In our study, ciprofloxacin (96.4%) and meropenem (95.5%) resistance rates for *A.baumannii* strains are particularly alarming and similar to the resistance patterns recorded in studies conducted in Türkiye. Colistin, tigecycline and piperacillin/tazobactam susceptibility profiles of *A.baumannii* could not be evaluated using the E-test method according to EUCAST criteria.

Studies have highlighted the role of *P.aeruginosa* in the pathogenesis of VAP, emphasizing its presence as a common pathogen in both early and late-onset VAP cases[13,14]. In a study conducted in Türkiye in which VAP agents were evaluated, cotrimoxazole resistance was found in 65.2% of *P.aeruginosa*. In another study conducted in our country, the ciprofloxacin resistance rate was 39% in *P.aeruginosa*[8]. In our study, the high resistance rate of *P.aeruginosa* to cotrimoxazole (94.1%) and ciprofloxacin (26.4%) is remarkable and reflects the trends observed in studies in our country[12]. The intrinsic resistance of *P.aeruginosa* to many antimicrobial agents underlines the difficulty in treating infections caused by this pathogen[15]. In our study, carbapenem resistance was relatively low in *P.aeruginosa* isolates. Although known to be effective against *P.aeruginosa* strains, empirical use of carbapenem group antibiotics is limited due to increasing resistance rates[16]. Resistance rates of *P.aeruginosa* strains isolated from ICU patients have been shown to be higher[17].

Multidrug resistant *K.pneumoniae* strains are common in cases of VAP, and these strains often produce extended-spectrum beta-lactamase (ESBL), especially the bla CTX-M-15 gene, which is common[18]. Ventilator-associated pneumonia due to multidrug-resistant *Klebsiella spp*. can be monobacterial or polybacterial, with polybacterial cases associated with higher mortality rates and distinct clinical characteristics[19]. In a study conducted in Türkiye, *K.pneumoniae* was found to be the 3rd most common VAP agent with 18.4%[20]. In our study, *Klebsiella spp*. strains, which ranked third in frequency (12.5%) among gram-negative strains, showed high resistance to multiple antibiotics, including ciprofloxacin (84.8%) and piperacillin/tazobactam (87.8%), consistent with ICU findings reported in the literature[4].

These resistance patterns in gram-negative agents require regular updating of local antibiograms to guide empirical treatment effectively. Due to our study's low colcystin resistance in gram-negative bacteria, colistin-containing regimens can be considered a priority in the empirical treatment plan of severe septic patients in our unit.

The resistance patterns of gram-positive bacteria, especially *S.aureus* and *coagulase-negative staphylococci*,

pose significant treatment challenges[21]. *S.aureus* is an important agent in nosocomial infection and community-acquired pneumonia, and methicillin resistance, which limits the efficacy of β-lactam antibiotics, is becoming increasingly common in nosocomial isolates[22]. There are, thus, problems with therapy, as methicillin-resistant strains could also be resistant to most other antibiotic groups[23]. The high resistance of *S.aureus* to oxacillin (71.4%) and ciprofloxacin (85.7%) found in our study emphasizes the importance of surveillance and infection control measures to prevent the spread of MRSA[24]. However, the lack of resistance to vancomycin, teicoplanin, and linezolid offers treatment options for these infections[25].

The Limitations of Study

This study has several limitations that should be acknowledged. First, its retrospective design and reliance on electronic health records may introduce selection bias or incomplete data, particularly regarding clinical outcomes such as mortality rates, treatment durations, or longitudinal follow-up. Second, the study's single-center nature limits our findings' generalizability to other ICUs with differing patient demographics, antibiotic stewardship protocols, or regional resistance patterns. Third, excluding polymicrobial cultures and contaminated samples, while necessary to ensure analytical clarity, may overlook clinically relevant co-infections or complex microbiological interactions encountered in real-world ICU settings. Additionally, certain antibiotics (e.g., colistin, tigecycline) could not be evaluated due to methodological constraints (e.g., EUCAST criteria), which may affect the interpretation of susceptibility profiles for critically important therapeutic agents.

Our results provide valuable information about VAP agents' epidemiology and resistance profiles in intensive care units. These data are critical for guiding empirical antibiotic therapy and implementing effective infection control measures. Furthermore, the high prevalence of multidrug-resistant (MDR) pathogens in this study's endotracheal aspirates from intensive care unit patients emphasizes the need for strict surveillance, appropriate antimicrobial stewardship and effective infection control practices. Additional multicentre studies are warranted to monitor antimicrobial resistance trends and develop strategies to combat these challenging pathogens.

References

1. Pickens C, Wunderink R. Methicillin-resistant staphylococcus aureus hospital-acquired pneumonia/ventilator-associated pneumonia. Seminars in Respiratory and Critical Care Medicine. 2022;43(02):304–309.
2. Hasan J, Nessa S, Rabbani R. Comparative evaluation of linezolid and teicoplanin in the treatment of ventilator-associated mrsa pneumonia: a single-center experience. International Journal of Infection. 2020;7(3).
3. Sharma A, Thakur A, Thakur N, Kumar V, Chauhan A, Bhardwaj N. Changing Trend in the Antibiotic Resistance Pattern of Klebsiella Pneumonia Isolated From Endotracheal Aspirate Samples of ICU Patients of a Tertiary Care Hospital in North India. Curēus 2023.
4. Büyüktuna SA, Hasbek M, Çelik C, Ünlüsavuran M, Avcı O, Baltacı S, et al. Yoğun Bakım Ünitesinde Gelişen Klebsiella pneumoniae Enfeksiyonları: Karbapenem Direnci ve Hasta Mortalitesi ile İlgili Risk Faktörler. Mikrobiyoloji Bülteni2020;54:378–391.
5. Fanning J, Panigada M, Bassi GL. Nosocomial Pneumonia in the Mechanically Ventilated Patient. Seminars in Respiratory and Critical Care Medicine. 2022;43:426–439.
6. Feng D-Y, Zhou Y-Q, Zou X-L, Zhou M, Zhu J-X, Wang Y-H, et al. Differences in microbial etiology between hospital-acquired pneumonia and ventilator-associated pneumonia: a single-center retrospective study in Guang Zhou Infection and Drug Resistance. 2019;Volume 12:993–1000.
7. Eggimann P, Revelly J-P. Should Antibiotic Combinations Be Used to Treat Ventilator-Associated Pneumonia? Seminars in Respiratory and Critical Care Medicine. 2006;27:068–081.
8. Şafak B, Çiftçi I-H, Kıyıldı N, Aktepe O-C, Çetinkaya Z, Altındiş M Ventilatör ilişkili pnömoni tanısında endotrakeal aspirat kültürleri:2004–2006 yılları sonuçları. 2007;21(2):81–85.
9. Dede B, Kadanalı A, Karagoz G, Comoglu S, Bektaşoğlu M, İrvem A Yoğun bakım ünitemizden gönderilen derin trakeal aspirat kültürlerinin değerlendirilmesi. 2014;54(1):15–20.
10. Sagmak-Tartar A, Ozer AB, Ulu R, Akbulut A. Microbiological Evaluation of the Pathogens Isolated From the Endotracheal Aspirate Samples of the Patients Followed in the Intensive Care Units: A One-Year Retrospective Analysis. Klimik Dergisi. 2018;:56–60.
11. Ameet H, Ankita A, Kumar G. Study of microbiological profile of ventilator associated pneumonia. Paripex Indian Journal Of Research. 2024;48–49.
12. Karakeçe E, Demiray T, Erdoğan F, Çiftci İH. Endotrakeal aspirat örneklerinden izole edilen gram-negatif etkenler. ACU Sağlık Bil Derg. 2014(3):200–203.
13. Raikod BRP, Awati A, Kinhal SV, Saraf N. Incıdence Of Pneumonıa In Crıtıcally Ill Patıents On Ventılator In Basaveshwar Teachıng And General Hospıtal. Journal of Evolution of Medical and Dental Sciences. 2014;3:13374–13379.

14. Golia S, T SK, L VC. Microbial Profile of Early and Late Onset Ventilator Associated Pneumonia in The Intensive Care Unit of A Tertiary Care Hospital in Bangalore, India. Journal of Clinical and Diagnostic Research 2013.
15. Tsubosa Y, Sato H, Bando E, Ota Y, Tanuma A, Ohmagari N. Relationship between the pathogens of postoperative pneumonia after an esophagectomy for thoracic esophageal cancer and the aggregate length of preoperative hospital stay. Esophagus2010;7:81–86.
16. Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: Results from the SENTRY Antimicrobial Surveillance Program, 2009–2012. International Journal of Antimicrobial Agents. 2014;43:328–334.
17. Tunçoğlu E, Yenişehirli G, Bulut Y. Klinik örneklerden izole edilen Pseudomonas aeruginosa suşlarında antibiyotik direnci, ANKEM Derg. 2009;23(2):54–8.
18. Mohamed ER, Aly SA, Halby HM, Ahmed SH, Zakaria AM, El-Asheer OM. Epidemiological typing of multidrug-resistant Klebsiella pneumoniae, which causes pediatric ventilator-associated pneumonia in Egypt. Journal of Medical Microbiology/Journal of Medical Microbiology. 2017;66:628–634.
19. Adukauskiene D, Ciginskiene A, Adukauskaite A, Koulenti D, Rello J. Clinical Features and Outcomes of VAP Due to Multidrug-Resistant Klebsiella spp.: A Retrospective Study Comparing Monobacterial and Polybacterial Episodes. Antibiotics. 2023;12:1056.
20. Duran H, Çeken N, Atik TK. Bacteria Isolated from Endotracheal Aspirate Samples and Antibiotic Resistance Rates:5-year Analysis:5-year Retrospective Analysis. Türkiye Klinikleri Tıp Bilimleri Dergisi. 2021;41:327–334.
21. Saha B, Bal M, S. Emergence of multi-drug resistant clinical strains of staphylococcus aureus. International Journal of Natural Sciences,. 2016;1–6.
22. Fatima S, Uddin M, Rao P, Rao S. Role of multidrug-resistant pathogens in ventilator-associated pneumonia in a tertiary care hospital in india. Avicenna Journal of Clinical Microbiology and Infection. 2022;9(2):49–54.
23. Elnasser Z, Obeidat H, Bani-Salem M, Amarin Z, Banni-Issa A, Kaplan N. Is methicillin-resistant staphylococcus aureus a common pathogen in ventilation-associated pneumonia?. Medicine. 2021;100(20).
24. Afzal M, Vijay AK, Stapleton F, Willcox M. The Relationship between Ciprofloxacin Resistance and Genotypic Changes in S. aureus Ocular Isolates. Pathogens. 2022;11:1354.
25. Jagadeesan U, Manavalan J, Sri Nsk R, Banaji N. Minimum inhibitory concentration levels of mupirocin by e-test among staphylococcus aureus isolates and their antimicrobial susceptibility pattern. International Journal of Pharmacy and Pharmaceutical Sciences 2023:24–27.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Tranexamic Acid in Total Knee Arthroplasty: A Comprehensive Examination of Double-Dose Strategies for Hemostasis

Total Diz Artroplastisinde Traneksamik Asit: Hemostaz için Çift Doz Stratejilerinin Kapsamlı Bir İncelemesi

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ABSTRACT

Aim: *The current study aimed to evaluate the impact of administering tranexamic acid (TXA) through intravenous (IV) or intraarticular (IA) routes, in double doses, in conjunction with postoperative drain clamping (DC), on postoperative bleeding, transfusion requirements, and thromboembolic complications in patients undergoing total knee arthroplasty (TKA).*

Material and Methods: *A retrospective review of 96 patients undergoing unilateral primary TKA for gonarthrosis between 2021 and 2022 was conducted. Patients received either double-dose IV TXA (n=52), double-dose IA TXA (n=26), or no TXA (n=18) along with postoperative DC. Various parameters were compared among groups, including preoperative and postoperative hemoglobin (Hb) levels, blood transfusion requirements, and length of hospital stay (LOS).*

Results: *Both IV and IA double-dose TXA significantly reduced postoperative bleeding compared to no TXA administration. The need for blood transfusion was lowest in the double-dose IV TXA group. No significant differences were observed in thromboembolic complications among the groups. Length of hospital stay (LOS) was significantly shorter in the TXA groups compared to the no TXA group.*

Conclusions: *Administration of double-dose TXA, either IV or IA and postoperative DC effectively reduced postoperative bleeding in TKA patients. Double-dose IV TXA demonstrated the lowest transfusion rates, suggesting a potential advantage in reducing transfusion requirements. Both IV and IA TXA administrations were safe and efficacious, with no significant increase in thromboembolic complications, emphasizing their overall safety profile in TKA patients.*

Key words: *total knee arthroplasty; double-dose tranexamic acid; transfusion rate*

ÖZET

Amaç: *Bu çalışma, total diz artroplastisi (TDA) uygulanan hastalarda, intravenöz (IV) veya intra-artiküler (IA) yollarla çift dozda uygulanan traneksamik asidin (TXA) ve ameliyat sonrası dren klempajının (DC), ameliyat sonrası kanama, transfüzyon gereksinimleri ve tromboembolik komplikasyonlar üzerindeki etkisini değerlendirmeyi amaçladı.*

Gereç ve Yöntem: *2021 ve 2022 yılları arasında gonartroz nedeniyle tek taraflı primer TDA uygulanan 96 hastanın retrospektif bir incelemesi yapıldı. Hastalar, çift doz IV TXA (n=52), çift doz IA TXA (n=26) veya TXA uygulanmayan (n=18) gruplarına ayrıldı ve ameliyat sonrası DC uygulandı. Preoperatif ve postoperatif hemoglobin (Hb) seviyeleri, kan transfüzyon gereksinimleri ve hastanede kalış süresi (HKS) gibi çeşitli parametreler gruplar arasında karşılaştırıldı.*

Bulgular: *Hem IV hem de IA çift doz TXA, TXA uygulanmayan gruba kıyasla ameliyat sonrası kanamayı önemli ölçüde azalttı. Kan transfüzyon gereksinimi en düşük olan grup çift doz IV TXA grubuydu. Gruplar arasında tromboembolik komplikasyonlarda anlamlı bir fark gözlenmedi. Traneksamik asit gruplarında, TXA uygulanmayan gruba kıyasla HKS anlamlı ölçüde daha kısaydı.*

Sonuç: *Çift doz TXA'nın, IV veya IA olarak uygulanması ve ameliyat sonrası DC ile birlikte, TDA hastalarında ameliyat sonrası kanamayı etkili bir şekilde azalttığı tespit edildi. Çift doz IV TXA, en düşük transfüzyon oranlarını gösterdi ve transfüzyon gereksinimlerini azaltmada potansiyel bir avantaj sundu. Hem IV hem de IA TXA uygulamaları güvenli ve etkili bulundu, tromboembolik komplikasyonlarda anlamlı bir artış olmaması, TDA hastalarında genel güvenlik profilini vurgulamaktadır.*

Anahtar kelimeler: *total diz protezi; çift doz traneksamik asit; transfüzyon oranı*

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Introduction

Total knee arthroplasty (TKA) is a frequently conducted surgery to address severe knee joint degeneration. The primary objective of prosthesis implementation is to facilitate normal kinematics and joint range of motion. Despite the medial pivot knee prosthesis (MPTKP) simulating natural knee kinematics, a consensus on the prosthesis that completely represents these characteristics has yet to be developed[1]. Enhancing patient safety and satisfaction during and post-TKA is crucial. Despite significant advancements in anaesthetic and surgical methodologies, TKA continues to be linked with substantial perioperative blood loss[2]. Total knee arthroplasty would trigger the fibrinolysis system, potentially resulting in significant haemorrhage[3]. Allogenic blood transfusion carries the risk of negative outcomes, including hemolytic responses, antigenic responses, transfusion-related severe kidney failure, and cardiovascular problems. These complications may lead to costly burdens and possibly fatal consequences for patients[4]. So far, many techniques have been used to reduce blood loss, such as pharmaceutical therapy, autologous donation, and allogenic transfusions of blood[5]. Furthermore, other techniques have been effectively used to manage bleeding, minimize blood loss, and reduce the need for transfusions after surgery. These procedures include the use of drain clamping (DC), the administration of tranexamic acid (TXA), and the application of tourniquets[6,7].

Prior research has shown that the intravenous (IV) and intraarticular (IA) applications of TXA effectively decrease blood loss and the need for transfusions in primary TKA without elevating the risk of thrombosis[8]. Drain clamping is a suggested technique to minimize blood loss during the initial postoperative phase after TKA. The frequent application of clamps to drains used in TKA has been supported by several individuals; however, it continues to be an issue of dispute even among physicians who continue to employ postoperative drains[7,9,10]. Various methods have been reported to minimize the loss of blood and the requirement for blood transfusions after TKA. However, the most effective approach is still uncertain. Both DC and TXA treatments are relevant to us as straightforward approaches to hemostasis[11]. Nevertheless, the studies published so far have not reached a unanimous agreement regarding the IV or IA dosage of TXA in TKA. The objective of the study was to examine the impact of TXA administration and the different methods of administration (double dose IV or double dose IA) on the overall blood loss and blood volume in the drains (1), the need for blood transfusion (2), and the occurrence of thromboembolic complications (3) in patients undergoing TKA with postoperative DC.

Material and Methods

Following obtaining ethical approval from the local ethics committee (approval date: 13/02/2024, approval number: 2024/03-75), a thorough retrospective review was carried out by examining hospital records by scanning. Written informed consent was obtained from all participants, thereby ensuring voluntary participation and authorization to utilize their anonymized data in the current study. The current study included patients who underwent unilateral primary TKA for gonarthrosis between 2021 and 2022. Inclusion criteria comprised patients aged between 50 and 85 years, with a preoperative hemoglobin level of ≥11 g/dL, and with at least one year of follow-up data. Patients were excluded if they underwent bilateral or revision TKA, had active infections, hematological disorders such as coagulopathies, or significant cardiovascular complications. The study was conducted by the principles outlined in the Declaration of Helsinki.

To ensure the reliability of the results, potential confounding factors were minimized by excluding patients with known coagulopathies, hematological disorders, or significant cardiovascular diseases, as these conditions were part of the exclusion criteria. However, minor comorbidities not meeting exclusion thresholds, such as controlled hypertension or type 2 diabetes mellitus, were documented and adjusted for during data analysis when necessary. Anticoagulants or antiplatelet medications were discontinued at least seven days before surgery, as per institutional protocols, and patients with deviations from these protocols were excluded.

A retrospective investigation was conducted to examine the impact of various administration methods of TXA (double dose IV administration or double dose IA administration) on bleeding in 96 patients who underwent unilateral primary TKA for gonarthrosis between 2021 and 2022. Preoperative haemoglobin (Hb) levels, postoperative Hb levels (postoperative 8th hour, 24th hour, and 72nd hour), need for blood transfusion, and length of hospital stay (LOS) were compared among each other and with patients who did not receive TXA. The IV administration of TXA was conducted as a gradual infusion 30 minutes before the surgical procedure.

The dosage of the application was established at 15 mg/kg TXA. A duplicate dosage of TXA was administered 15 minutes before the release of the tourniquet. In IA administration, following the closure of the arthrotomy, a dosage of 30 mg/kg of TXA (double dose) was administered into the joint after diluting it with 10 ml of saline. This entire volume was carefully injected into the joint space after ensuring the injection did not exceed the joint's maximum injectable capacity. The technique was standardized to maintain consistency across patients.

The same surgeons performed the surgical procedures, utilizing tourniquets and haemovac drains. The haemovac drains remained closed for 2 hours during the postoperative phase. Subsequently, the drains were opened, and the bleeding volume was observed for 24 hours. The drains were removed 24 hours after the surgery. Each patient received a standard surgical procedure, including a midline incision, medial parapatellar arthrotomy, and unilateral TKA. The criterion for blood transfusion was a postoperative Hb level <8 g/dL. All patients were monitored for one year after the surgery to detect potential complications. Patients were monitored for thromboembolic complications for one year postoperatively. In cases where clinical findings raised suspicion of deep vein thrombosis (DVT) or pulmonary embolism (PE), Doppler ultrasonography and computed tomography angiography (CTA) were performed to confirm the diagnosis. Routine follow-ups included clinical evaluations at 1, 6, and 12 months, during which patients were assessed for symptoms such as leg swelling, pain, or shortness of breath, which could indicate potential thromboembolic events.

Statistics

The statistical analyses in the study were conducted using the IBM Statistical Package for Social Sciences (SPSS) program version 22 (IBM Corp., Armonk, NY, USA). An assessment was conducted to determine the conformity of the parameters to a normal distribution using the Shapiro-Wilks test. Descriptive statistical methods were employed, such as mean, standard deviation, and frequency. The Student t-test was used to compare two groups for parameters with a normal distribution, while the Mann-Whitney U test was employed for parameters without a normal distribution. The Wilcoxon Signed Ranks test was employed to compare parameters within the same group that did not exhibit a normal distribution. The Fisher-Freeman-Halton test was used to compare qualitative data. The significance level was assessed at $p < 0.05$.

Table 1. *Patient characteristics and postoperative data*

		Min-Max	Mean ± SD
Age		52–81	66.44±4.03
Blood collected in the drain (cc)		300–1200	512.5±212, 88 (400)
Length of stay		3–6	3.78±0.67 (4)
		n	%
Gender	Female	80	83.3
	Male	16	16.7
Tranexamic acid use	Absent	18	18.8
	Intraarticular	26	27.1
	Intravenous	52	54.2
Transfusion requirement	Yes	12	12.5
	No	84	87.5

Table 2. *Haemoglobin levels in the general participants*

Haemoglobin	Min-Max	Mean ± SD (median)
Preoperative	10–16	12.41±1.25 (13)
Postoperative 8th hour	9–14	10.65±1.13 (11)
Postoperative 24th hour	8–12	9.49±1.11 (9)
Postoperative 72nd hour	6–12	9±1.15 (9)

Results

The patients' ages varied from 52 to 81 years, averaging 66.44±4.03. The majority of the patients (83.3%) were female, while the remaining 16.7% were male. Out of the total of 96 patients, a double dosage of IV TXA was administered to 52 patients, a double dose of IA TXA was administered to 26 patients, and no TXA was administered to 18 patients. The mean amount of time for LOS was estimated to be 3.78±0.67 days. No instances of DVT or PE were found in any patient. 12.5% of patients needed blood transfusions, whereas 87.5% did not necessitate them (Table 1).

The average Hb assessments of the patients before the surgery and 72 hours after the surgery are shown in Table 2. Upon analyzing the Hb values based on the administration of TXA, there was no notable disparity between the groups at the 8th hour after surgery. However, at the 24th and 72nd hours after surgery, the Hb values of patients who were not administered TXA were considerably lower than those who were administered TXA ($p<0.05$). No significant differences were

Table 3. *Parameters that vary according on tranexamic acid's usage or administration method*

	Tranexamic acid use			
	Absent	Intraarticular	Intravenous	p
	(Min-Max)-(Mean ± SD)	(Min-Max)-(Mean ± SD)	(Min-Max)-(Mean ± SD)	
Age	(61–73)-(65.67±2, 83)	(52–81)-(66.85±5, 11)	(60–79)-(66.5±3, 8)	[1]0.630
Blood collected in the drain (cc)	(400–1200)-(677.78±315.4 (500))	(300–1000)-(476.92±181.79 (400))	(400–1000)-(473.08±152.26 (400))	[3]0.015*
Length of stay	(4–6)-(4.44±0.62 (4))	(3–5)-(3.69±0.62 (4))	(3–5)-(3.6±0.57 (4))	[3]0.000*
Preoperative	(10–16)-(12.5±1.69 (13))	(10–15)-(12.38±1.13 (12))	(10–15)-(12.38±1.14 (13))	0.948
Post-operative 8th hour	(9–14)-(10.5±1.54 (10))	(9–13)-(10.58±1.14 (10))	(9–13)-(10.73±0.97 (11))	0.403
Post-operative 24th hour	(8–11)-(8.67±1.14 (8))	(8–12)-(9.62±1.2 (9))	(8–11)-(9.71±0.94 (10))	0.001[3]
Post-operative 72nd hour	(6–9)-(7.67±0.91 (8))	(7–12)-(9.19±1.27 (9))	(7–11)-(9.37±0.79 (9))	0.000[3]
Preoperative-postoperative 8th hour p[4]	0.000*	0.000*	0.000*	
Preoperative-postoperative 24th hour p[4]	0.000*	0.000*	0.000*	
Preoperative-postoperative 72nd hour p[4]	0.000*	0.000*	0.000*	
	n (%)	n (%)	n (%)	
Gender				
Female	15 (83%, 3)	21 (80%, 8)	44 (84%, 6)	[1 2]0.932
Male	3 (16%, 7)	5 (19%, 2)	8 (15%, 4)	
Transfusion requirement				
Yes	7 (38%, 9)	4 (15%, 4)	1 (1%, 9)	-
No	11 (61%, 1)	22 (84%, 6)	51 (98%, 1)	

[1]Student t Test; [2]Fisher Freeman Halton Test; [3]Mann-Whitney U Test; [4]Wilcoxon Sign Test; *p<0.05
The number of intravenous tranexamic acid administrations in those who required transfusion was not suitable for statistical comparison due to being only 1.

observed between IV and IA applications when comparing them in various periods (p>0.05) (Table 3).

The amount of blood extracted from the haemovac drain in patients who did not receive TXA was considerably greater than that of patients who received IA and IV TXA (p1:0.021; p2:0.031; p<0.05). The current study found no significant difference in the quantity of blood extracted from the haemovac drain between patients who had IA and IV TXA doses (p>0.05) (Table 3).

The LOS values of those who did not receive TXA were shown to be considerably greater than those who received IA and IV TXA (p1:0.002; p2:0.000; p<0.05). The LOS values did not show any statistically significant difference between patients who received IA and IV TXA treatments (p>0.05) (Table 3).

Upon analyzing the need for transfusion among the different groups, it was shown that only 1 out of 52 patients who received IV TXA needed a transfusion, whereas 4 out of 26 patients who received IA TXA required a transfusion, and 7 out of 18 patients who were not administered TXA needed a transfusion (Table 3). Statistical analysis was not possible due to the small sample size of one patient needing transfusion in the IV TXA group.

Discussion

The study's key discovery was that using IV or IA double-dose TXA, in conjunction with postoperative DC, effectively decreased postoperative bleeding at comparable rates. Furthermore, when assessing the need for blood transfusion during the postoperative period, it was noticed that the administration of double-dose IV TXA resulted in the lowest transfusion rates. Although a statistical analysis could not be conducted, this finding suggests a potential benefit of double-dose IV TXA in reducing the need for transfusion. Both applications demonstrated high safety and efficacy in terms of complications and overall safety.

A substantial body of literature supports the use of IV TXA in TKA. In a study conducted by Akgül et al.[12],

it was found that administering 20 mg/kg of IV TXA before the skin incision within primary TKA resulted in a significant decrease in total blood loss and reduced drainage volume, as in line with the current study. In a retrospective study conducted by Pitta et al.[7], involving 610 patients over 4 years, it was observed that the IV administration of TXA led to a notable reduction of 9.4% in blood loss during TKA. However, no significant difference was observed in the incidence of DVT between the TXA and the control groups. Topical delivery of TXA has gained increasing attention as a means to avoid bleeding, particularly when compared to the safety issues associated with IV administration. With a systemic absorption rate of less than 70%, it is a potential option for systemic use. In a randomized controlled study by Ishida et al.[13], a group of patients undergoing TKA were injected with 2000 mg/20 mL of topical TXA, while another group received a placebo. The results showed a significant reduction in postoperative Hb levels in the TXA group compared to the control group, similar to the findings in the present study.

Several studies have shown the use of varying dosages of TXA during the perioperative phase of TKA to achieve improved outcomes[14–16]. The Mohammad meta-analysis[17] found that administering high doses of IV TXA (≥2 g or ≥30 mg/kg as a single push) resulted in decreased transfusion needs in comparison with standard doses (≤1 g TXA), as in line with the current study. However, the impact on thromboembolic complications and mortality remained unclear. A study conducted by A. Fígar et al.[18] revealed that administering one single injection (1 g) of IV TXA effectively decreased the need for transfusion following total hip arthroplasty while maintaining a low incidence of adverse events. In a study conducted by Kang et al.[19], it was shown that administering three doses (3 g) of IV TXA following TKA in older patients resulted in lower blood loss, less postoperative inflammation, and fewer fibrinolytic responses compared to a single dosage (1 g) or two doses (2 g). Importantly, this treatment approach did not lead to increased adverse events. A recently published randomized controlled trial demonstrated that the single-dose schedule was as effective as the two-dose strategy[20]. Based on the findings of a meta-analysis performed in 2023[21], it was concluded that the blood transfusion rate did not differ significantly between the single-dose and double-dose TXA groups. Within the existing literature, there is a noticeable lack of reference to the various modalities of administration (IV or IA) of high-dose (double-dose) TXA despite several cases comparing different TXA dosages. The current investigation examined different ways of administering high-dose TXA (IV or IA) to address this research gap. The current study determined that the double IV dose of TXA was the most effective approach to reducing transfusion rates.

Several recent studies have compared the effectiveness of combining DC with TXA administration for controlling bleeding after TKA. Chareancholvanich et al.[22] discovered that the combination of DC and TXA administration resulted in a substantial decrease in postoperative bleeding and blood transfusion following TKA, compared to utilizing TXA or DC individually, as in line with the current study. In theory, DC may provide transient hemostasis by providing a tamponade impact in the joint, reducing blood loss and decreasing the need for transfusion[23]. In addition, Sangasoongsong et al.[24] discovered that using a relatively low dosage of TXA in conjunction with a 2-hour DC technique successfully decreased postoperative bleeding and the need for transfusions in traditional TKA. The current research examines several administration techniques for a double dosage of TXA combined with a 2-hour DC technique. Consequently, significant enhancements were observed in postoperative bleeding and transfusion rates, which aligns with the existing literature.

The LOS is a significant factor in determining the overall expenses associated with TKA surgery. According to a meta analyse[21], administering a double-dose of TXA may decrease the LOS following joint arthroplasty[25–27]. Nevertheless, only three studies in the meta-analysis documented LOS, rendering the aggregated data somewhat contentious. Additional research is required to validate these findings. Moreover, the aggregated findings indicated no substantial difference in the LOS between those receiving double doses and those receiving single doses[21]. In the current investigation, we observed that the administration of double dosage TXA with postoperative DC greatly reduced the LOS time, according to the literature. Furthermore, as a contribution to the existing body of research, we found that the LOS remained similar regardless of whether the double dosage of TXA was administered IV or IA.

Limitations and Strengths

The data presented in this study are limited, as is common for any research conducted using a retrospective data review. First, the data was not collected systematically or prospectively. Second, all the subjects included

in the research were exclusively managed at a single facility in Türkiye. Third, the absence of a comprehensive long-term follow-up may result in underestimating potential complications. Fourth, the analysis did not consider the cost burden of using double-dose TXA. A significant limitation of the study is the failure to compare the additional cost associated with double-dose TXA with the potential cost savings resulting from reduced LOS. As a result, a comprehensive conclusion could not be drawn.

Moreover, using a specific criterion, such as a Hb value below 8 g/dL, as a transfusion threshold, it is evident that this current research may provide varying interpretations on transfusion rates compared to other publications available in the field that use different criteria. This study focused solely on evaluating double-dose TXA via intravenous and intraarticular routes without direct comparison to single-dose TXA. This design choice limits the generalizability of our findings regarding dose-specific efficacy. Future studies with larger sample sizes and direct comparisons between single- and double-dose regimens are warranted to validate and expand upon these results. Also, the study employed a 2-hour drain clamping duration, which differs from the 3-hour duration used in some previous studies, such as Chareancholvanich et al. This discrepancy in timing was based on institutional protocols and surgeon preference. However, the potential impact of different clamping durations on outcomes was not systematically investigated, representing a limitation of this study. The study's relatively small sample size limited the ability to perform robust statistical analyses for transfusion rates, particularly in subgroup comparisons. This limitation reduces the generalizability and statistical power of the findings related to transfusion requirements. The study's most influential conclusion is that administering high-dose (double-dose) TXA, either IV or IA, in conjunction with postoperative DC has beneficial effects on postoperative bleeding and the need for transfusions. This work addresses the existing knowledge gap in the literature by investigating several methods for administering a double dosage of TXA using the postoperative DC approach.

Conclusion

The study found that utilizing IV or IA double dosage TXA and postoperative DC significantly reduced postoperative bleeding at similar rates. In addition, during the evaluation of blood transfusion requirements in the postoperative period, it was observed that a double dose of IV TXA led to the lowest transfusion rates. This finding indicates a potential advantage of using a double dose of IV TXA to decrease the requirement for transfusion. Both applications showcased exceptional safety and efficacy, with no complications and a strong focus on overall safety.

Conflicts of Interest

The authors have no conflicts of interest to declare relevant to this article's content.

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Ethics Approval

The study was approved by the local institutional ethical review board of the local ethics committee (Firat University Ethics Committee) (approval date: 13/02/2024, approval number: 2024/03–75).

Informed Consent

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

References

1. Karahan M, Acar E, Serarslan U, Gültekin A. Medial pivot total knee arthroplasty: Mid-term results. Acta Orthop Belg. 2023;89:97–102.
2. Fan D, Ma J, Liu X, Zhang L. Peri-articular administration of tranexamic acid is an alternative route in total knee arthroplasty: a systematic review and meta-analysis. J Orthop Surg Res. 2022;17(1):211.
3. Sadigursky D, Araujo LM, Fernandes RJC. Efficacy of tranexamic acid in reducing blood loss in total knee arthroplasty. Acta Ortop Bras. 2018;26:63–6.
4. DeMik DE, Carender CN, Glass NA, Brown TS, Callaghan JJ, Bedard NA. Who is still receiving blood transfusions after primary and revision total joint arthroplasty? J Arthroplasty. 2022;37(6s):S63–9.
5. Conteduca F, Massai F, Iorio R, Zanzotto E, Luzon D, Ferretti A. Blood loss in computer-assisted mobile bearing total knee arthroplasty. A comparison of computer-assisted surgery with a conventional technique. Int Orthop. 2009;33:1609–13.
6. Kumar A. Perioperative management of anemia: limits of blood transfusion and alternatives to it. Cleve Clin J Med. 2009;76 Suppl 4:S112–S118.

7. Pitta M, Zawadsky M, Verstraete R, Rubinstein A. Intravenous administration of tranexamic acid effectively reduces blood loss in primary total knee arthroplasty in a 610-patient consecutive case series. Transfusion. 2016;56:466–71.
8. Ling T, Zhang L, Huang L. The efficacy and safety of combined administration of intravenous and intra-articular tranexamic acid in total knee arthroplasty: An update meta-analysis. J Clin Pharm Ther. 2022;47(9):1312–1321.
9. Wu Y, Yang T, Zeng Y, Li C, Shen B, Pei F. Clamping drainage is unnecessary after minimally invasive total knee arthroplasty in patients with tranexamic acid: A randomized, controlled trial. Medicine (Baltimore) . 2017;96:e5804.
10. Migliorini F, Maffulli N, Betsch M, Eschweiler J, Tingart M, Baroncini A. Closed suction drainages in Lower Limb Joint Arthroplasty: A level I evidence based meta-analysis. Surgeon. 2022;20(3):e51–e60.
11. Han YH, Huang HT, Pan JK, Zeng LF, Liang GH, Liang HD, et al. Is the combined application of both drain-clamping and tranexamic acid superior to the single use of either application in patients with total-knee arthroplasty?: A meta-analysis of randomized controlled trials. Medicine (Baltimore) . 2018;97(36):e11573.
12. Akgül T, Büget M, Salduz A, Edipoğlu İS, Ekinci M, Küçükay S, et al. Efficacy of preoperative administration of single high dose intravenous tranexamic acid in reducing blood loss in total knee arthroplasty: A prospective clinical study. Acta Orthop Traumatol Turc. 2016;50:429–31.
13. Ishida K, Tsumura N, Kitagawa A, Hamamura S, Fukuda K, Dogaki Y, et al. Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. Int Orthop. 2011;35:1639–45.
14. Chen JY, Chin PL, Moo IH, Pang HN, Tay DK, Chia SL, et al. Intravenous versus intra-articular tranexamic acid in total knee arthroplasty: A double-blinded randomised controlled noninferiority trial. Knee. 2016;23:152–56.
15. Sun Q, Li J, Chen J, Zheng C, Liu C, Jia Y. Comparison of intravenous, topical or combined routes of tranexamic acid administration in patients undergoing total knee and hip arthroplasty: a meta-analysis of randomised controlled trials. BMJ Open. 2019;9:e024350.
16. Han X, Gong G, Han N, Liu M. Efficacy and safety of oral compared with intravenous tranexamic acid in reducing blood loss after primary total knee and hip arthroplasty: a meta-analysis. BMC Musculoskelet Disord. 2018;19:430.
17. Hmidan Simsam M, Delorme L, Grimm D, Priestap F, Bohnert S, Descoteaux M, et al. Efficacy of high dose tranexamic acid (TXA) for hemorrhage: A systematic review and meta-analysis. Injury. 2023;54:857–70.
18. Fígar A, Mc Loughlin S, Slullitel PA, Scordo W, Buttaro MA. Influence of single-dose intravenous tranexamic acid on total hip replacement: A study on transfusions, collateral complications, and readmissions. Einfluss einer intravenösen Einzelgabe von Tranexamsäure auf die Implantation einer Hüfttotalendoprothese: Eine Studie zu Transfusionen, kolateralen Komplikationen und Rehospitalisierungen. Orthopade. 2017;46:359–65.
19. Kang BX, Li YL, Xu H, Gao CX, Zhong S, Zhang J, et al. Effect of Multiple Doses of Intravenous Tranexamic Acid on Perioperative Blood Loss in Total Knee Arthroplasty: A Randomized Controlled Study. Orthop Surg. 2021;13:126–33.
20. Sershon RA, Fillingham YA, Abdel MP, Malkani AL, Schwarzkopf R, Padgett DE, et al. The Optimal Dosing Regimen for Tranexamic Acid in Revision Total Hip Arthroplasty: A Multicenter Randomized Clinical Trial. J Bone Joint Surg Am. 2020;102:1883–90.
21. Yang YZ, Cheng QH, Zhang AR, Yang X, Zhang ZZ, Guo HZ. Efficacy and safety of single- and double-dose intravenous tranexamic acid in hip and knee arthroplasty: a systematic review and meta-analysis. J Orthop Surg Res. 2023;18:593.
22. Chareancholvanich K, Siriwattanasakul P, Narkbunnam R, Pornrattanamaneewong C. Temporary clamping of drain combined with tranexamic acid reduce blood loss after total knee arthroplasty: a prospective randomized controlled trial. BMC Musculoskelet Disord. 2012;20;13:124.
23. Kiely N, Hockings M, Gambhir A. Does temporary clamping of drains following knee arthroplasty reduce blood loss? A randomised controlled trial. Knee. 2001;8:325–27.
24. Sa-Ngasoongsong P, Wongsak S, Chanplakorn P, Woratanarat P, Wechmongkolgorn S, Wibulpolprasert B, et al. Efficacy of low-dose intra-articular tranexamic acid in total knee replacement;a prospective triple-blinded randomized controlled trial. BMC Musculoskelet Disord. 2013;14:340.
25. Wilde JM, Copp SN, McCauley JC, Bugbee WD. One dose of intravenous tranexamic acid is equivalent to two doses in total hip and knee arthro plasty. J Bone Joint Surg Am. 2018;100:1104–9.
26. Charette RS, Bernstein JA, Sloan M, Nchako CM, Kamath AF, Nelson CL. One versus two doses of intravenous tranexamic acid in total knee arthroplasty. J Knee Surg. 2021;34:749–54.
27. Golz AG, Yee HK, Davis BJ, Adams WH, Brown NM. One dose versus two doses of intravenous tranexamic acid in total joint arthroplasty. J Am Acad Orthop Surg. 2021;29:e555–62.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Should Cholecystectomy be Performed Simultaneously with Bariatric Surgery in Obesity Patients?

Obezite Hastalarında Kolesistektomi Bariyatrik Cerrahi ile Eşzamanlı Yapılmalı mı?

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ABSTRACT

Introduction: *Asymptomatic cholelithiasis may be detected in the tests performed while obese patients are being prepared for surgery. Determining whether asymptomatic gallstones will cause enough symptoms after bariatric surgery to cause the patient to undergo cholecystectomy surgery will help in the decision to perform concomitant cholecystectomy. This study aimed to determine whether there is a marker to determine whether patients with preoperative cholelithiasis are likely to undergo cholecystectomy after bariatric surgery.*

Material and Methods: *We retrospectively reviewed the files of 771 patients who underwent bariatric surgery for obesity in the Gastroenterology Surgery Clinic of a Tertiary Training and Research Hospital between January 2015 and November 2023. Patients with cholelithiasis before bariatric surgery were included in Group 1 if they had undergone cholecystectomy surgery after bariatric surgery and in Group 2 if they had not.*

Results: *Cholelithiasis was detected in 168 (21.8%) of 771 patients whose charts were reviewed. Group 1 included 73 patients who had undergone cholecystectomy after bariatric surgery, and Group 2 included 90 patients who had not undergone cholecystectomy. There were significant differences between the two groups in terms of age, gender, height-weight ratio, hemoglobin, total cholesterol, low and high-density lipoprotein, triglycerides, gallbladder stone diameter (p=0.395, 0.828, 0.584, 0.660, 0.316, 0.461, 0.988, 0.476, 0.208, respectively).*

Discussions: *Our study found that asymptomatic gallstones required surgery twice as often as in the general population. Age, gender, height-weight ratio, hemoglobin, total cholesterol, low and high-density lipoprotein, triglycerides, and gallbladder stone diameter did not affect asymptomatic gallstones becoming symptomatic to require surgery. Obese patients undergo cholecystectomy surgery after bariatric surgery at a much higher rate than the general population. Therefore, cholecystectomy simultaneously with bariatric surgery should be considered as an option in these patients.*

Key words: *bariatric surgery; cholecystectomy; obesity*

ÖZET

Giriş: *Obezite hastalarında yeterli kilo verimi sağlanamadığında bariyatrik cerrahi yöntemler uygulanmaktadır. Bu hastalar ameliyata hazırlanırken yapılan tetkiklerde asemptomatik kolelithiazis saptanabilmektedir. Asemptomatik kolelithiazisin, bariyatrik cerrahisi sonrasında hastanın kolesistektomi ameliyatı geçirmesine neden olacak kadar semptoma yol açıp açmayacağını belirlemek eşzamanlı kolesistektomi yapılması kararının verilmesine yardımcı olacaktır. Bu çalışmanın amacı kolelithiazis saptanan hastaların bariyatrik cerrahi sonrası kolesistektomi geçirme olasılığını belirleyecek bir belirteç olup olmadığını saptamaktır.*

Gereç ve Yöntem: *Ocak 2015 ile Kasım 2023 arasında Üçüncü Basamak Eğitim Araştırma Hastanesi Gastroenteroloji Cerrahisi Kliniğinde obezite nedeni ile bariyatrik cerrahi uygulanan 771 hastanın dosyaları retrospektif olarak tarandı. Bariyatrik cerrahi öncesinde kolelithiazis tespit edilen hastalar eğer bariyatrik cerrahi sonrasında kolesistektomi ameliyatı geçirmişlerse Grup 1'e, geçirmemişlerse Grup 2'ye dâhil edildiler.*

Bulgular: *Dosyası taranan 771 hastanın 168'inde (%21,8) kolelithiazis tespit edildi. Bariyatrik cerrahi sonrası kolesistektomi ameliyatı geçirmiş olan 73 hasta Grup 1'e, kolesistektomi ameliyatı geçirmemiş olan 90 hasta Grup 2'ye dâhil edildi. İki grup arasında yaş, cinsiyet, boy kilo oranı, hemoglobin, total kolesterol, düşük ve yüksek dansiteli lipoprotein, trigliserit, safra kesesi taş çapı açısından anlamlı farklılık saptanmadı (sırasıyla p=0,395, 0,828, 0,584, 0,660, 0,316, 0,461, 0,988, 0,476, 0,208)*

Tartışma: *Çalışmamızda asemptomatik safra kesesi taşlarının topluma göre iki kat daha yüksek oranda cerrahi gerektirdiğini saptadık. İki grup arasında yaş, cinsiyet, boy kilo oranı, hemoglobin, total kolesterol, düşük ve yüksek dansiteli lipoprotein, trigliserit, safra kesesi taş çapı açısından anlamlı fark olmaması, bu faktörlerin asemptomatik safra kesesi taşlarının ameliyata neden olacak kadar semptomatik hale gelmesinde bir etkileri olmadığını olmadığını göstermekteydi. Kolelithiazis tespit edilen obezite hastalarının bariyatrik cerrahi sonrası safra kesesi ameliyatı olup olmayacaklarını önceden öngörmek mümkün görünmese de bu hastalar bariyatrik cerrahi sonrasında topluma göre çok daha yüksek oranda kolesistektomi ameliyatı geçirmektedirler. Bu nedenle bu hastalarda bariyatrik cerrahi ile eş zamanlı olarak kolesistektomi ameliyatı yapılması bir seçenek olarak göz önünde bulundurulmalıdır.*

Anahtar kelimeler: *bariyatrik cerrahi; kolesistektomi; obezite*

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Introduction

Obesity is an epidemic disease with increasing prevalence all over the world, decreasing the life quality of individuals and causing a large number of morbidities[1]. Effective weight loss can be achieved through lifestyle changes and adjustments in eating habits[2–4]. When weight loss cannot be achieved with these methods, bariatric surgery methods come to the fore[5]. In patients who are candidates for bariatric surgery, tests are performed before surgery to determine whether there is an obstacle to surgery. During these examinations, diseases that have not shown any symptoms before can be detected[6–8]. Gallstones are among these diseases. While 80% of gallstones detected incidentally in the community remain silent and do not require treatment, 20% require treatment[9]. There is no consensus among surgeons on the treatment of symptomatic gallstones[10]. Watchful waiting, administration of ursodeoxycholic acid, extracorporeal shock-wave lithotripsy, or cholecystectomy may be preferred in managing symptomatic gallstones[10,11]. Cholecystectomy is one of the most common operations in general surgery practice[12]. However, some authors suggest that concurrent cholecystectomy with bariatric surgery may cause morbidities ranging from prolonged hospitalization to mortality[13,14]. Another group of authors suggests that cholecystectomy can be safely performed simultaneously after appropriate port placement[15].

Considering these different opinions, determining whether asymptomatic gallstones will cause enough symptoms after bariatric surgery to cause the patient to undergo cholecystectomy surgery will help the surgeon decide whether to perform cholecystectomy concurrently with bariatric surgery. In this study, we aim to determine whether patients with preoperative cholelithiasis have a marker to determine the likelihood of undergoing cholecystectomy after bariatric surgery.

Materials and Methods

The Ethics Committee approved the study (E-71522473–050.01.04–31897_405). Subsequently, this study was conducted. For this retrospective study, the files of 771 patients admitted to the Gastroenterology Surgery Clinic of the Third Level Training and Research Hospital for obesity and who underwent sleeve gastrectomy (SG) between January 2015 and November 2023 were retrospectively reviewed. Age, gender, weight, Body Mass Index (BMI), total cholesterol, hemoglobin, triglyceride, high and low-density lipoprotein values, abdominal ultrasonographic examination findings at the time of admission and stone diameter if there was a stone in the gallbladder were extracted from the files of the patients. Patients with gallstones were included in Group 1 if they had undergone cholecystectomy after SG and in Group 2 if not.

Exclusion Criteria: Patients younger than 18 years, patients without gallbladder stones before sleeve gastrectomy surgery, and patients who underwent cholecystectomy surgery before or concurrent with SG.

Surgical Technique

All operations are performed by one of the three consultant surgeons. Surgical intervention was performed in the French position [16]. We placed thirty-eight French orogastric bougie per-oraly and subsequently freed omentum from the stomach. Surgeons transected the greater curvature using laparoscopic staplers. In cases in which cholecystectomy was performed simultaneously with bariatric surgery, cholecystectomy was performed by entering an additional trocar from the right lower quadrant of the abdomen when necessary.

Statistical Analysis

All analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program software version 23.0 (IBM Corp., Armonk, NY, USA). We used The Kolmogorov-Smirnov test to evaluate whether the distributions of numerical variables were normal. Information on the general characteristics of the study population was provided with descriptive analyses. We used the Student-T test to analyze parametric numeric variables and the Mann Whitney-U test to analyze nonparametric variables. We used the Chi-Square test for categorical data analysis. The non-numerical variables were presented as percentages and counts. While the normally distributed numeric variables were presented as mean and standard deviation, the numeric variables that were not normally distributed were presented as median (minimum-maximum). The $p<0.05$ level was considered statistically significant.

Results

Gallbladder stones were detected in 168 (21.8%) of 771 patients whose files were reviewed. Since 5 of 168 patients underwent cholecystectomy during SG, these patients were excluded from the study. A hundred and

Table 1. *Demographic variables*

		Group 1 (n=73)	Group 2 (n=90)	p Value
Age		33 (20–63)	36 (18–61)	0.395*
Gender	Female	61 (44.2%)	77 (55.8%)	0.828**
	Male	12 (48%)	13 (52%)	
Height		165 (154–175)	166 (154–181)	0.412*
Weight		138 (115–170)	138 (115–184)	0.941*
Body Mass Index		50 (41–68)	49 (40–69)	0.584*

* The Mann-Whitney U Test, ** The Chi-Square Test

Table 2. *Statistical analysis regarding patients variables*

		Group 1 (n=73)	Group 2 (n=90)	p Value
Hemoglobin		13.32±1.52	13.2±1.54	0.660*
Cholesterol		201.19±36.3	207.02±36.731	0.316*
Low-density lipoprotein		135.25±28.06	138.87±32.45	0.461*
High-density lipoprotein		45 (30–71)	45 (28–82)	0.988**
Trigliserite		162 (77–461)	147 (70–548)	0.476**
Diameter of gallstone	Multiple, millimetric gallstones	30 (55.6%)	24 (44.4%)	0.208***
	<1 cm	18 (36.7%)	31 (63.3%)	
	1–2 cm	20 (42.6%)	27 (57.4%)	
	>2 cm	4 (33.3%)	8 (66.7%)	

* The Independent Samples T-test, ** The Mann-Whitney U test, *** The Chi-Square test

sixty three patients were included in the study. Seventy three of 163 patients (45%) had undergone cholecystectomy after SG. The 73 patients who had undergone cholecystectomy after sleeve gastrectomy were included in Group 1, and 90 patients who had not undergone cholecystectomy were included in Group 2.

The interval between sleeve gastrectomy surgery and cholecystectomy surgery was 382 (13–2586) days in patients included in Group 1.

The patients' median age in the study was 35 (18–63) years, while the patients' median ages in group 1 and group 2 were 33 (20–63) and 36 (18–61) years, respectively. We did not find a significant statistical difference between the groups regarding age (p=0.395) (Table 1).

Of the patients included in the study, 25 were male, and 138 were female. Of the female patients, 61 (44.2%) were in group 1 and 77 (55.8%) were in group 2. Of the 25 male patients, 12 (48%) were in group 1 and 13 (52%) were in group 2. We did not find significant statistical differences between the groups regarding gender distribution (p=0.828) (Table 1).

The median height of the patients included in the study was 166 (154–181), the median height of the patients in Group 1 was 165 (154–175), and the median height of the patients in Group 2 was 166 (154–181). There was no statistically significant difference between the groups regarding height (p=0.412) (Table 1).

The median weight of the patients included in the study was 138 (115–184). The median weight of the patients in Group 1 was 138 (115–170), and the median weight in Group 2 was 138 (115–184). We did not find a significant statistical difference between the groups regarding weight (p=0.941) (Table 1).

The median BMI of the patients in the study was 50 (40–69). The median BMI of the patients in Group 1 was 50 (41–68), and the median BMI in Group 2 was 49 (40–69). We did not find a significant statistical difference between the groups in terms of (BMI) (p=0.584) (Table 1).

The mean hemoglobin values of the patients in the study were 13.25±1.52, and the mean hemoglobin values in Group 1 and Group were 13.31±1.52 and 13.21±1.54, respectively. We did not find significant

statistical differences between the groups regarding hemoglobin values (p=0.660) (Table 2).

The mean cholesterol values of the patients included in the study were 204.36±36.55, and those in Group 1 and Group 'were 201.19±36.34 and 207.02±36.73, respectively. We did not find a significant statistical difference between the groups regarding cholesterol values (p=0.316) (Table 2).

The mean Low-density lipoprotein (LDL) values of the patients included in the study were 137.19±30.45, and the mean LDL values of the patients in Group 1 and Group 'were 135.25±28.06 and 138.87±32.45, respectively. We did not find significant statistical differences between the groups regarding LDL value (p=0.461) (Table 2).

The median High-density lipoprotein (HDL) values of the patients included in the study were 45 (28–82). The median HDL values of the patients in Group 1 were 45 (30–71), and the median HDL values of the patients in Group 2 were 45 (28–82). No statistically significant difference was found between the groups regarding HDL values (p=0.988) (Table 2).

The median triglyceride values of the patients included in the study were 151 (70–548), 162 (77–461) for the patients in Group 1, and 147 (70–548) for the patients in Group 2. We did not find a statistically significant difference between the groups regarding triglyceride values (p=0.476) (Table 2).

Discussion

With the extensive use of ultrasonography, gallstones are now detected in 10–15% of the population[17]. Our study group found that the prevalence of cholelithiasis was approximately twice as high as this rate. Although many factors play a role in the etiology of cholelithiasis, obesity is effective in gallbladder stone formation[18]. One of the most important reasons why the frequency of cholelithiasis was twice as high in our study group compared to healthy individuals may be because the study was conducted in obese patients.

In addition to obesity, conditions that facilitate gallbladder stone formation have been described in the literature. A sedentary lifestyle, diabetes mellitus, family history, high-calorie diet, and female gender are among these conditions[19]. In their study conducted in 2001, Kama et al. reported that 75% of the individuals with gallstones were women[20]. Our study found that a much higher proportion (85%) of patients with gallstones were women. Although obesity is more common in the male gender, it is known that women have a higher body fat percentage than men[21]. High body fat is a predisposing factor for many gastrointestinal diseases and gallstones[22]. The fact that our study was conducted in obese patients and women have a higher body fat ratio may explain the much higher incidence of gallstones in women in our study. In addition to the female gender, advanced age is a risk factor for gallstone formation[23]. The patients with gallstones in our study were in the young age group, which is in contrast with the literature, but the fact that our study was conducted in obese patients may explain this contrast. All of our patients were obese or super obese. As discussed above, this factor significantly affects the incidence of gallstones, which is higher than that of the general population. However, the lack of significant difference in height, weight, and BMI between the two groups suggests that height, weight, and BMI do not affect asymptomatic gallstones becoming symptomatic enough to warrant surgery.

Along with obesity, hyperlipidemia is another important factor that plays an important role in gallstone formation. Hypercholesterolemia, low HDL levels, and hypertriglyceridemia have been shown to facilitate the formation of gallstones[24,25]. In a study conducted by Sheng B et al. in 2022, they found that high weight decreased the rate of gallstone detection in patients with hypercholesterolemia. In the same study, effective control of hypercholesterolemia was much more effective than weight control in managing asymptomatic gallstones[26]. Our study found that cholesterol, HDL, LDL and triglyceride levels were ineffective in asymptomatic gallstones becoming symptomatic. However, the fact that the rate of asymptomatic gallstones becoming symptomatic enough to cause surgery was approximately two times higher in our patient group compared to the general population suggests that cholecystectomy should also be performed during bariatric surgery in obese patients with asymptomatic gallstones.

In general, weight loss reduces the formation of gallstones, but a loss of more than 25% of body weight or a weight loss of 1.5 kg/week has the opposite effect[27]. Rapid weight loss has an effect on asymptomatic gallstones becoming symptomatic. The literature has determined that this is caused by increased lipolysis due to rapid weight loss, gallbladder hypomotility due to decreased nutrition, and bile concentration[28–29]. Our

study is compatible with the literature. However, this compatibility is due to blood cholesterol levels.

The limitations of this study are its retrospective nature and the lack of information on weight loss and changes in blood cholesterol levels after bariatric surgery.

Conclusion

Although it is not possible to predict whether obese patients with gallstones will undergo gallbladder surgery after bariatric surgery, these patients undergo cholecystectomy surgery after bariatric surgery at a much higher rate than the general population. Therefore, cholecystectomy simultaneously with bariatric surgery should be considered as an option in these patients.

References

1. Gönüllü E, Yüksel A, Coşkun M, Harmantepe T, Fırtına G, Karaman K. Oversewing the Staple Line: Does It Safe to Prevent Leakage? J Laparoendosc Adv Surg Tech A. 2024;34(2):120–126.
2. Astbury NM, Piernas C, Hartmann-Boyce J, Lapworth S, Aveyard P, Jebb SA. A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss. Obes Rev. 2019;20:569–587.
3. Sooriyaarachchi P, Jayawardena R, Pavey T, King NA. A low-calorie meal replacement improves body composition and metabolic parameters in shift workers with overweight and obesity: a randomized, controlled, parallel group trial. Nutr Metab. 2024;21:32.
4. Anuk T, Köksal N, Avşar F, Allahverdi TD, Sülü B, Çakmur H. Our initial results related to bariatric surgery. Ege J Med. 2017;56:82–85.
5. Bindal V, Agarwal P, Khaitan M, Prasad A, Peters ANC, Narwaria M, et al. An Indian multicentre real-world study on long-term quality of life outcomes following bariatric surgery. Clin Obes. 2024;e12693.
6. Alshaikh AA, Mahmood SE, Riaz F, Assiri AS, Abdulrahman MA, Asiri MYA, et al. Knowledge of Diabetes Mellitus and Practices Regarding Lifestyle Factors and Diabetes Management in a General Adult Population of Aseer Region, Saudi Arabia. Diabetes Metab Syndr Obes. 2024;17:2775–2787.
7. Patel A, Abu Dayyeh BK, Balasubramanian G, Hinton A, Krishna SG, Brethauer S, et al. The impact of bariatric surgery on admissions for gastrointestinal complications and conditions associated with obesity: A nationwide study. World J Surg. 2024;48:175–185.
8. Yıldız Ş, Alphan E, Batar N. Comparison of eating attitudes and behaviors and body mass index changes in patients who had undergone sleeve gastrectomy. Kafkas J Med Sci. 2020;10:136–144.
9. Patel H, Jepsen J. Gallstone Disease: Common Questions and Answers. Am Fam Physician. 2024;109:518–524.
10. Shenoy R, Kirkland P, Hadaya JE, Tranfield MW, DeVirgilio M, Russell MM, et al. Management of symptomatic cholelithiasis: a systematic review. Syst Rev. 2022;11:267.
11. Portincasa P, Di Ciaula A, Wang HH, Moschetta A, Wang DQ-H. Medicinal treatments of cholesterol gallstones: old, current and new perspectives. Curr Med Chem. 2009;16:1531–1542.
12. Fehring L, Brinkmann H, Hohenstein S, Bollmann A, Dirks P, Pölitz J, et al. Timely cholecystectomy: important factors to improve guideline adherence and patient treatment. BMJ Open Gastroenterol. 2024;11(1):e001439.
13. Hamad GG, Ikramuddin S, Gourash WF, Schauer PR. Elective cholecystectomy during laparoscopic Roux-en-Y gastric bypass: is it worth the wait? Obes Surg. 2003;13:76–81.
14. Worni M, Guller U, Shah A, Gandhi M, Shah J, Rajgor D, et al. Cholecystectomy concomitant with laparoscopic gastric bypass: a trend analysis of the nationwide inpatient sample from 2001 to 2008. Obes Surg. 2012;22:220–229.
15. Lee J-H, Han G, Kim YJ, Jung M-S, Choi D. A Technique for Simultaneous Cholecystectomy During Bariatric Surgery. JSLS. 2015;19(4):e2015. 00072.
16. Trelles N, Gagner M. Sleeve Gastrectomy. Operative Techniques in General Surgery. 2007;9:123–131.
17. Gurusamy KS, Samraj K. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Cochrane Database Syst Rev. 2006;30(6): CD005440.
18. Erlinger S. Gallstones in obesity and weight loss. Eur J Gastroenterol Hepatol. 2000;12:1347–1352.
19. Velidedeoğlu M, Kaya B. Asemptomatik safra kesesi taşı olan hastalarda kolesistektomi gerçekten gerekli mi? Haydarpasa Numune Med J. 2015;55(3):196–200.
20. Kama NA, Doganay M, Dolapci M, Reis E, Atli M, Kologlu M. Risk factors resulting in conversion of laparoscopic cholecystectomy to open surgery. Surg Endosc. 2001;15:965–968.
21. Muscogiuri G, Verde L, Vetrani C, Barrea L, Savastano S, Colao A. Obesity: a gender-view. J Endocrinol Invest. 2024;47:299–306.
22. Kim MS, Song M, Kim S, Kim B, Kang W, Kim JY, et al. Causal effect of adiposity on the risk of 19 gastrointestinal diseases: a Mendelian randomization study. Obesity. 2023;31:1436–1444.
23. Ozkan E, Yildiz MK, Cakir T, Gunay E, Eris C, Dulundu E, et al. Outcome analysis of laparoscopic cholecystectomy in patients 65 years and older. Ulus Cerrahi Derg. 2012;28:88.
24. Kurtul N, Pençe S, Kocoglu H, Aksoy H, Capan Y. Serum lipid and lipoproteins in gallstone patients. Acta Medica. 2002;45:79–81.
25. Völzke H, Baumeister SE, Alte D, Hoffmann W, Schwahn C, Simon P, et al. Independent risk factors for gallstone formation in a region with high cholelithiasis prevalence. Digestion. 2005;71:97–105.
26. Sheng B, Zhao Q, Ma M, Zhang J. An inverse association of weight and the occurrence of asymptomatic gallbladder stone disease in hypercholesterolemia patients: a case-control study. Lipids Health Dis. 2020;19:228.
27. Li VK, Pulido N, Fajnwaks P, Szomstein S, Rosenthal R, Martinez-Duartez P. Predictors of gallstone formation after bariatric surgery: a multivariate analysis of risk factors comparing gastric bypass, gastric banding, and sleeve gastrectomy. Surg Endosc. 2009;23(7):1640–4.
28. Boerlage, T. C. C., Haal, S., Maurits de Brauw, L. et al. Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery: study protocol for a randomized controlled trial (UPGRADE trial) . BMC Gastroenterol 17, 164(2017)
29. Stokes, Caroline Sarah, and Frank Lammert. "Excess Body Weight and Gallstone Disease. " Visceral medicine vol. 37, 4(2021):254–260.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Relationship Between Knee Osteoarthritis Severity, Muscle Strength, Proprioception, and Quality of Life

Diz Osteoartriti Şiddeti, Kas Kuvveti, Propriyosepsiyon ve Yaşam Kalitesi Arasındaki İlişki

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ABSTRACT

Aim: *This study investigated the relationship between the severity of knee osteoarthritis (OA) and key clinical factors such as muscle strength, proprioception, and quality of life (QoL) in individuals with bilateral knee OA.*

Material and Methods: *A cross-sectional observational study was conducted with 40 participants diagnosed with bilateral knee OA. Isometric quadriceps and hamstring muscle strength were measured using a hand-held dynamometer. Proprioception was assessed using a digital inclinometer during knee flexion at 30° and 60°. Osteoarthritis severity was determined using the Kellgren-Lawrence classification and the Lequesne Algofunctional Knee Index, while QoL and functional status were evaluated using the WOMAC Index.*

Results: *As OA severity increased, significant increases were observed in WOMAC pain, stiffness, and physical function scores, indicating worse outcomes in QoL ($p<0.05$). Proprioception was notably impaired at 60° of knee flexion in the non-dominant leg as OA grade increased. At the same time, no significant muscle strength decline in the quadriceps and hamstrings was observed across OA grades ($p>0.05$).*

Conclusions: *OA severity is closely associated with worse QoL outcomes, particularly in pain and physical function, but not consistently with muscle strength. These findings highlight the need for rehabilitation programs that improve proprioception and pain management in OA patients.*

Key words: *osteoarthritis severity; osteoarthritis grade; knee proprioception; life quality; WOMAC; knee muscle strength*

ÖZET

Amaç: *Bu çalışma, bilateral diz osteoartriti (OA) olan bireylerde diz OA şiddeti ile kas kuvveti, propriyosepsiyon ve yaşam kalitesi gibi temel klinik faktörler arasındaki ilişkiyi araştırmayı amaçlamıştır.*

Gereç ve Yöntem: *Bilateral diz OA tanısı konan 40 katılımcı ile kesitsel bir gözlemsel çalışma yapılmıştır. İzometrik kuadriseps ve hamstring kas kuvveti, elle tutulan bir dinamometre kullanılarak ölçüldü. Propriyosepsiyon, 30° ve 60°'de diz fleksiyonu sırasında dijital bir inklinometre kullanılarak değerlendirildi. Osteoartrit şiddeti, Kellgren-Lawrence sınıflandırması ve Lequesne algofonksiyonel diz indeksi kullanılarak belirlenirken, yaşam kalitesi ve fonksiyonel durum WOMAC endeksi kullanılarak değerlendirildi.*

Bulgular: *OA şiddeti arttıkça, WOMAC ağrısı, sertlik ve fiziksel fonksiyon skorlarında anlamlı artışlar gözlenmiştir, bu da yaşam kalitesinde daha kötü sonuçları gösterir ($p <0,05$). Propriyosepsiyon, OA derecesi arttıkça dominant olmayan bacaktaki 60° diz fleksiyonunda önemli ölçüde bozuldu. Aynı zamanda, OA derecelerinde kuadriseps ve hamstringlerde belirgin bir azalma gözlenmemiştir. ($p >0,05$).*

Sonuç: *Diz osteoartriti şiddeti, özellikle ağrı ve fiziksel fonksiyonda daha kötü yaşam kalitesi ile yakından ilişkilidir, ancak kas kuvveti ile ilişkili değildir. Bu bulgular, OA hastalarında propriyosepsiyonun geliştirilmesi ve ağrı yönetimine odaklanan rehabilitasyon programlarının önemini vurgulamaktadır.*

Anahtar kelimeler: *osteoartrit şiddeti; osteoartrit derecesi; diz propriyosepsiyonu; yaşam kalitesi; WOMAC; diz kas kuvveti*

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Introduction

Knee osteoarthritis (OA) is a degenerative joint disease characterized by the breakdown of articular cartilage and changes in subchondral bone, leading to pain, stiffness, and functional limitations. It is one of the most prevalent musculoskeletal disorders, particularly affecting the elderly population, and is a leading cause of disability worldwide and in our country[1]. The rising prevalence of knee OA with advancing age significantly affects the quality of life, often leading to reduced mobility, increased pain, and psychological distress [2].

There is growing evidence that osteoarthritis severity, particularly in the knee joint, is closely related to declines in muscle strength, particularly in the quadriceps and hamstrings. Studies have consistently shown that individuals with more severe OA tend to have significantly reduced muscle strength, which exacerbates joint instability and contributes to worsening symptoms such as pain and functional limitations[3]. This reduction in muscle strength is primarily attributed to both disuse and the catabolic effects of chronic inflammation on muscle tissue, further worsening physical function and increasing the risk of falls[4]. The quadriceps, in particular, play a vital role in knee joint stability, and weakness in this muscle group has been shown to correlate strongly with the progression of OA and with the severity of pain and stiffness experienced by patients. Therefore, strengthening interventions targeting the quadriceps and hamstrings are essential components of rehabilitation aimed at improving joint function and quality of life (QoL) in individuals with OA[5].

Proprioception, or the ability to sense the position and movement of the joints, is another factor often impaired in individuals with knee OA. This impairment can decrease balance and coordination, exacerbating functional limitations and increasing the risk of falls[6]. Proprioceptive deficits have been linked to reduced muscle strength, joint instability, and increased joint pain, all of which contribute to the decline in physical function and QoL in OA patients[7].

The impact of knee OA on health-related quality of life is multifaceted, encompassing physical, psychological, and social dimensions. Chronic pain, functional limitations, and reduced mobility can lead to psychological issues such as depression and anxiety, further diminishing quality of life[2]. Additionally, OA is associated with other comorbidities such as obesity, cardiovascular disease, and diabetes, which further complicate disease management and reduce life quality[3].

The relationship between OA severity and life quality is well-documented, with more severe radiographic changes correlating with greater functional impairment and lower life quality scores[1]. However, it is not only the structural changes in the joint that determine the patient's experience; the psychological and emotional aspects, such as coping mechanisms and social support, also play a significant role[2]. Recent studies have emphasized the need for a holistic approach to managing OA that addresses the disease's physical and psychological aspects[8,9].

Our study was conducted to address the growing need for understanding the intricate relationship between osteoarthritis severity and muscle strength, particularly in the quadriceps and hamstrings, proprioception and QoL. Our study explores the differences in knee muscle strength, proprioception, and QoL in individuals with bilateral knee OA and examines the relationship between these factors and OA severity.

Material and Methods

Study Design and Setting

This cross-sectional observational study was conducted between 1 October 2023 and 30 July 2024 at the Physical Medicine and Rehabilitation Unit of Atatürk University and Erzurum City Hospital. The Erzurum Technical University institutional review board approved the study protocol (ethic code: 06.09.2023, 10–2), and all participants provided written informed consent before inclusion in the study. Our study was conducted by the Declaration of Helsinki.

Participants

A total of 40 individuals with bilateral knee osteoarthritis (age 58.25±6.19 years, height 167.8±6.53 cm, weight 84.12±4.89 kg) were recruited for this study. Participants were selected based on the following inclusion criteria:

- Diagnosed with bilateral knee osteoarthritis (both extremities are the same grade) as per clinical and radiological findings.
- No psychological, mental, or neurological disorders.
- No lower extremity injuries in the last six months.
- Patients were excluded if they had systemic inflammatory conditions or other comorbidities that could affect the outcome measures.

Variables and Data Collection

Muscle Strength Measurement: Isometric hamstring and quadriceps muscle strength were measured using a hand-held dynamometer (La Fayette). Before the assessment, participants were seated with their hips and knees at 90° flexion to ensure a standardized and stable testing posture. The dynamometer was placed just above the ankle for quadriceps measurements and at the back of the lower leg for hamstring measurements. Participants were instructed to exert maximal isometric contraction against the dynamometer for 3 to 5 seconds. Three trials were performed for each muscle group, and the average force (in Newtons) was recorded. Adequate rest (approximately 1–2 minutes) was provided between trials to minimize fatigue[10].

Proprioception Assessment: Proprioception was assessed using a dual inclinometer through an active angle repetition test. The participants were actively moved into the reference positions (30° and 60°) and were asked to replicate these positions with their eyes closed[11]. A digital inclinometer (J-Tech Medical, Midvale, UT, USA) was used for precise measurement. Three trials were conducted, and the average position error for both knees was calculated. Proprioception measurements were taken before muscle strength assessments.

Osteoarthritis Severity: Knee X-rays were evaluated by a physical medicine and rehabilitation specialist according to the Kellgren-Lawrence classification[12]. Osteoarthritis severity was also determined using the Lequesne Algofunctional Knee Index, which evaluates pain, walking ability, and functional limitations in daily activities. Higher scores on this index indicate more functional impairment.

Quality of Life and Functional Status: The WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) assessed participants' quality of life and knee function. The WOMAC consists of three main sections and 24 questions assessing pain, stiffness, and physical function. Higher WOMAC scores indicate worse outcomes in all domains (pain, stiffness, and physical function)[13].

Procedures

Participants were given detailed verbal and visual explanations of the study procedures during the initial session. Each participant underwent a 5-minute warm-up with stretching exercises before the assessments. The warm-up consisted of dynamic stretching exercises targeting the quadriceps, hamstrings, and calf muscles**,** each performed for 30 seconds and repeated twice for a total warm-up duration of 5 minutes**.** The rationale for this protocol was to enhance muscle flexibility and joint mobility before testing. Demographic data, including age, gender, height, weight, and dominant leg, were recorded. After the warm-up, participants were verbally and visually informed about the measurement procedures, and proprioception and muscle strength assessments were performed in that order. All measurements were conducted by a physiotherapist with 15 years of experience in the field.

Statistical Analysis

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS) program software version 20. Means, standard deviations, medians, and minimum-maximum values were calculated for the data. The chi-square test was used to compare categorical variables between groups. Pearson or Spearman correlation coefficients were calculated to assess the relationship between muscle strength, proprioception, and severity of osteoarthritis. A p-value of <0.05 was considered statistically significant.

Results

A total of 40 participants (45% male, 55% female) were included in the study, with an average age of 58.25±6.19 years, a minimum age of 45 years, and a maximum age of 80 years. The average body weight was 84.12±4.89 kg, with a median of 85 kg, a minimum of 55 kg, and a maximum of 111 kg. The participants' average height was 167.8±6.53 cm, with a minimum height of 150 cm and a maximum height of 190 cm. The duration of symptoms varied, with participants reporting an average duration of 5.70±4.9 years, a minimum of 1 year, and a maximum of 15 years (Table 1).

Table 1. *Demographic Information*

n: 40 (18 m, 22f)	Mean ± SD	Median	Min-Max
Age (years)	58.25±6.19	61	45–80
Body weight (kg)	84.12±4.89	85	55–111
Height (cm)	167.8±6.53	170	150–190
Duration of symptoms (years)	5.70±4.9	5	1–15

SD: Standart deviation, Min: Minimum, Max: Maximum

Table 2. Correlations of parameters (Spearman's rho)

Correlations																				
			ationofSympt	Age	Height	Body Weight	NDS-Quadriceps	DS-Quadriceps	NDS-Hamstring	DS-Hamstring	Lequesne	WomacPain	WomacStiffness	VOMACPhysicalFunctio	WOMACTotal	NDS Prop3	ND Prop60	DS Prop30	DS Prop60
earman's r	Duration of Symptoms	r	1	0,595	0,153	-.878**	0,051	-0,096	0,209	0,019	0,198	0,085	.752*	-0,166	-0,057	-.665*	-0,561	.665*	-.761*
		p	.	0,069	0,672	0,001	0,889	0,793	0,562	0,958	0,584	0,815	0,012	0,646	0,876	0,036	0,092	0,036	0,011
	Age	r		1	0,203	-0,038	-0,144	-0,181	-0,12	-0,114	0,271	0,032	0,277	0,132	0,143	-0,106	0,174	.393*	-0,252
		p		.	0,21	0,818	0,394	0,29	0,485	0,509	0,09	0,844	0,083	0,415	0,378	0,539	0,31	0,018	0,139
	Height	r			1	.313*	.475**	.405*	0,313	0,314	-0,193	-0,159	-0,259	-0,077	-0,156	0,044	0,14	0,18	-0,013
		p			.	0,049	0,003	0,014	0,063	0,063	0,233	0,327	0,107	0,637	0,335	0,797	0,415	0,293	0,941
	Body Weight	r				1	0,309	0,185	0,17	.362*	-.421**	-0,105	-.353*	-0,03	-0,095	0,053	-0,303	-0,185	0,218
		p				.	0,063	0,279	0,323	0,03	0,007	0,521	0,025	0,854	0,561	0,757	0,073	0,279	0,202
	NDS- Quadriceps	r					1	.702**	.758**	.654**	-0,233	0,049	-0,175	0,071	0,064	-0,182	-0,242	-0,227	-0,146
		p					.	0	0	0	0,166	0,772	0,3	0,674	0,706	0,288	0,155	0,184	0,397
	DS- Quadriceps	r						1	.682**	.682**	-.546**	-0,321	-.354*	-0,224	-0,28	0,064	0,064	-0,282	0,005
		p						.	0	0	0,001	0,056	0,034	0,189	0,099	0,713	0,713	0,095	0,977
	NDS-Hamstring	r							1	.757**	-0,233	0,001	-0,085	0,09	0,047	0,019	-0,149	-0,266	-0,285
		p							.	0	0,172	0,995	0,623	0,603	0,785	0,911	0,386	0,118	0,092
	DS-Hamstring	r								1	-0,244	-0,176	-0,202	-0,143	-0,137	-0,07	-0,083	-0,296	-0,209
		p								.	0,151	0,306	0,237	0,404	0,427	0,685	0,632	0,079	0,221
	Lequesne	r									1	.754**	.744**	.668**	.740**	-0,313	-0,071	0,02	-.573**
		p									.	0	0	0	0	0,063	0,683	0,909	0
	WomacPain	r										1	.626**	.893**	.923**	-0,276	-.362*	-0,264	-.577**
		p										.	0	0	0	0,103	0,03	0,12	0
	WomacStiffness	r											1	.659**	.740**	-.413*	0,04	0,003	-.703**
		p											.	0	0	0,012	0,819	0,987	0
	WOMAC Physical Function	r												1	.977**	-0,175	-0,105	-0,254	-.468**
		p												.	0	0,307	0,543	0,136	0,004
	WOMAC Total	r													1	-0,31	-0,149	-0,188	-.552**
		p													.	0,065	0,385	0,272	0
	NDS Prop30	r														1	.361*	0,03	.522**
		p														.	0,031	0,864	0,001
	NDS Prop60	r															1	.341*	0,258
		p															.	0,042	0,128
	DS Prop30	r																1	0,216
		p																.	0,206
	DS Prop60	r																	1
		p																	.
** Correlation is significant at the 0.01 level (2-tailed).																			
* Correlation is significant at the 0.05 level (2-tailed).																			

A strong negative correlation was observed between symptom duration and body weight (r=-0.878, p<0.01). This suggests that body weight tends to decrease as the duration of symptoms increases. This could indicate that patients with more prolonged osteoarthritis symptoms may experience weight loss, potentially due to reduced mobility or other factors related to disease progression. Additionally, a moderate positive correlation exists between the duration of symptoms and WOMAC physical function scores (r=0.752, p=0.012). This indicates that longer symptom duration is associated with worse physical function, as measured by the WOMAC scale (Table 2).

The Lequesne index is significantly positively correlated with several WOMAC components, including WOMAC Pain (r=0.754, p<0.01), WOMAC Stiffness (r=0.744, p<0.01), WOMAC Physical Function (r=0.668, p<0.01) and WOMAC Total (r=0.740, p<0.01). These strong positive correlations suggest that higher Lequesne scores indicate worse osteoarthritis severity and are strongly associated with worse pain, stiffness, physical function, and overall WOMAC scores.

Body weight negatively correlates with several WOMAC and Lequesne scores (r=-0.421, p<0.01). These negative correlations suggest that patients with higher body weight tend to have lower Lequesne and WOMAC scores, which might imply less severe osteoarthritis symptoms or better physical function in this cohort.

The Lequesne Index, which measures the severity of osteoarthritis, showed a statistically significant difference between the groups (p<0.01). Group 4 had the highest average score (10.11), indicating worse symptoms, while Group 3 had a lower score (7.81).

WOMAC Pain: There was a significant increase in pain severity with higher osteoarthritis grades (p<0.01). Group 2 reported the lowest pain scores (3.40), while Group 4 reported the highest (7.33). WOMAC Stiffness was also significantly worse in the higher grade groups (p<0.05), with group 4 showing the most severe stiffness (2.85). A strong, significant deterioration in WOMAC Physical Function with increasing osteoarthritis severity (p<0.01). Group 4 had the most impaired function (29.00) compared to Group 2 (12.20). The total WOMAC score, combining pain, stiffness, and function, was significantly higher in groups 4 (39.18) and 3 (36.34) compared to group 2.00 (16.80) (p<0.01).

Table 3. *Relationship between osteoarthritis severity and other parameters*

N: 40	Grade 2 (Mean ± SD)	Grade 3 (Mean ± SD)	Grade 4 (Mean ± SD)	Chi-Square	p-value
Duration of symptoms	5.2±2.9	5.88±3.54	6.24±2.55	-	-
Age (Years)	54.40±7.64	60.58±10.12	53.67±10.34	0.611	0.435
Height (cm)	170.80±7.53	164.62±7.33	161.78±15.43	2.893	0.089
Body weight (kg)	87.20±8.53	84.88±9.04	80.22±19.32	0.088	0.767
NDS quadriceps (Nm)	25.53±11.28	21.59±6.36	23.24±8.58	0.017	0.895
DS quadriceps (Nm)	21.23±5.05	19.32±5.08	22.03±8.00	0.623	0.430
NDS hamstring (Nm)	16.79±6.79	14.34±7.55	13.94±1.54	0.010	0.921
DS hamstring (Nm)	15.17±4.14	13.68±4.13	13.18±3.56	0.846	0.358
Lequesne index	5.60±0.89	7.81±3.66	10.11±2.93	8.221	**0.004**
WOMAC pain	3.40±1.34	7.12±1.95	7.33±4.18	13.076	**0.001**
WOMAC stiffness	1.20±0.45	2.44±0.67	2.85±1.07	5.137	**0.023**
WOMAC physical function	12.20±3.38	26.77±4.91	29.00±6.24	12.267	**0.001**
WOMAC total	16.80±5.17	36.34±6.53	39.18±11.49	12.252	**0.001**
NDS proprioception 30°	2.50±0.58	2.17±1.89	2.92±1.39	1.120	0.290
NDS proprioception 60°	4.17±0.19	3.78±1.89	4.08±2.19	5.631	**0.018**
DS proprioception 30°	3.50±1.35	2.22±0.90	3.25±1.82	2.984	0.084
DS proprioception 60°	4.67±0.38	3.92±1.30	3.08±1.34	9.237	**0.002**

DS: Dominant side, NDS: Non-dominant side

US Proprioception at 60° showed a significant decrease with increasing osteoarthritis severity ($p<0.05$), with group 3 reporting a mean of 3.78 and group 4 a mean of 4.08, compared to 6.17 in group 2. AS Proprioception at 60° also demonstrated a significant decline ($p=0.002$), with group 4.00 showing the lowest score (3.08) compared to group 2.00 (6.67) (Table 3).

These results indicate that as osteoarthritis grade increases, patients experience significantly worse outcomes in pain, stiffness, physical function, and proprioception, particularly at larger joint angles (60°). Muscle strength did not show significant differences between the groups, suggesting that while quadriceps and hamstring strength may not directly correlate with osteoarthritis grade, functional impairment and proprioception are more closely associated with disease severity. The significant increase in WOMAC and Lequesne scores with higher grades of osteoarthritis further reinforces the impact of osteoarthritis on overall quality of life.

Discussion

Our study aimed to explore the relationship between osteoarthritis (OA) severity and muscle strength, proprioception, and overall quality of life. While the severity of osteoarthritis increased, no weakening of quadriceps and hamstring muscle strength was observed. As the severity of osteoarthritis increased, the WOMAC index, which measures pain, stiffness and physical function of the individuals, increased. Additionally, no proprioception deficit was observed on the dominant side but just the non-dominant side 60°.

The relationship between osteoarthritis (OA) severity and muscle strength, particularly in the quadriceps and hamstrings, has been explored extensively in recent literature. Numerous studies have demonstrated that individuals with more severe OA typically exhibit greater muscle weakness, which exacerbates functional limitations and increases disability[14,15]. Both the quadriceps and hamstring muscles play crucial roles in stabilizing the knee joint, and their weakening contributes to the progression of OA[16]. Quadriceps weakness, in particular, has been identified as a primary factor in the progression of OA. Studies show that lower quadriceps strength is associated with higher grades of OA, increased pain levels, and poorer functional outcomes. This weakness is often more pronounced in individuals with advanced radiographic stages of OA[3,15]. Moreover, a systematic review and meta-analysis found that lower knee extensor strength increases the risk of OA structural worsening, especially in women[15]. Although often less emphasized than quadriceps strength, hamstring

strength is also critical. Studies have shown that imbalances between hamstring and quadriceps strength (H/Q ratio) can further destabilize the knee joint, increasing the risk of joint damage. Targeted strengthening of both muscle groups, rather than just the quadriceps, has improved functional outcomes in individuals with OA[17,18]. As a result of our study, we found no decrease in muscle strength with osteoarthritis severity. Takagi et al.[19] emphasized in their study that knee muscle strength was associated with radiographic OA incidence but not with its progression. Additionally, while muscle strength is an essential factor for joint function, studies have also pointed out that muscle cocontraction patterns, proprioception, and neuromuscular control might contribute more to functional impairment in OA than just pure muscle strength alone. These findings imply that muscle strength may not always decrease linearly with increasing OA severity[20]. These results are parallel to our study.

The relationship between proprioception and OA severity has been well-documented in recent studies. Individuals with more severe OA tend to experience greater proprioceptive impairments, especially in joint position sense (JPS) and motion sense[21]. As OA progresses, proprioceptive accuracy decreases due to the degeneration of joint structures, including mechanoreceptors in the knee, which play a critical role in detecting joint position and movement[22,23]. This decline in proprioception is associated with increased functional limitations and a higher risk of falls due to reduced neuromuscular control[7]. Moreover, proprioceptive impairments have been correlated with increased pain and disability, as they reduce the ability to stabilize the knee joint during movement[24]. These impairments also exacerbate muscle weakness, particularly in the quadriceps, further compounding functional difficulties[25]. Considering the findings from our study, a significant reduction in proprioception was observed on just the non-dominant side of 60°. No changes were observed in the dominant extremity and other angles. Two research has found no significant difference in proprioceptive acuity between more and less painful knees in OA patients, indicating that proprioception may not directly correlate with the degree of OA-related joint deterioration[26,27]. This challenges the assumption that proprioception consistently worsens as OA progresses, suggesting that other factors, such as pain, muscle strength, or neuromuscular control, might play a more critical role in proprioceptive function. While proprioception may not always align with OA severity, it is still crucial in maintaining balance and preventing falls. Studies show that proprioceptive impairments may be more related to joint pain and instability than the radiographic severity of OA[27].

WOMAC is a validated tool widely used to assess patient-reported OA-related outcomes, particularly in the knees and hips. As OA severity increases, patients typically report higher WOMAC scores across all subscales (pain, stiffness, and physical function), correlating with worsening symptoms and disability[28,29]. Our study shows that patients with more severe radiographic OA tend to have significantly higher WOMAC scores, indicating greater impairment. This supports that OA's progression directly impacts quality of life, with pain and functional limitations being the most affected aspects. Furthermore, the WOMAC index is sensitive to even small changes in OA severity, making it a reliable tool for capturing the clinical significance of worsening symptoms[30]. The studies by Ribeiro et al.[9] and Khalil et al.[31] demonstrated a positive correlation between higher KL grades and elevated WOMAC scores, particularly in patients with moderate to severe OA. All these results are consistent with the results of our study.

A relatively small sample size (n=40) may limit the generalizability of the results to broader populations. Furthermore, while the study assessed both dominant and non-dominant sides for proprioception, it did not explore other potentially influential factors, such as physical activity levels, comorbidities, or variations in pain management that could affect the outcomes. Additionally, the reliance on self-reported measures like the WOMAC index, while valuable, can introduce subjective bias in assessing pain and functional impairment. The strengths of our study are the use of validated tools like the Kellgren-Lawrence classification, the Lequesne Algofunctional Knee Index, and the WOMAC index, which enhances the study's reliability and comparability with other research. Another strength is the standardization of measurement protocols for muscle strength and proprioception, which were performed by an experienced physiotherapist, ensuring consistency and minimizing measurement bias.

Conclusion

Our study has demonstrated that increasing osteoarthritis (OA) severity is strongly associated with higher WOMAC scores, indicating worsening pain, stiffness,

and physical function. Notably, while proprioception impairments were evident, they did not correlate uniformly with OA grade, suggesting that other factors may influence joint stability and balance. Despite these findings, muscle strength, particularly in the quadriceps and hamstrings, did not significantly decline across OA severity, highlighting the need for further research into the role of neuromuscular control in OA progression.

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References

1. Muraki S, Akune T, Oka H, et al. Association of radiographic and symptomatic knee osteoarthritis with health-related quality of life in a population-based cohort study in Japan: the ROAD study. Osteoarthritis and cartilage. 2010;18:1227–34.
2. Park HM, Kim HS, Lee YJ. Knee osteoarthritis and its association with mental health and health-related quality of life: a nationwide cross-sectional study. Geriatrics & Gerontology International. 2020;20:379–83.
3. Ruhdorfer A, Wirth W, Hitzl W, Nevitt M, Eckstein F, Investigators OI. Association of thigh muscle strength with knee symptoms and radiographic disease stage of osteoarthritis: data from the Osteoarthritis Initiative. Arthritis care & research. 2014;66:1344–53.
4. Khalaj N, Abu Osman NA, Mokhtar AH, Mehdikhani M, Wan Abas WAB. Balance and risk of fall in individuals with bilateral mild and moderate knee osteoarthritis. PloS one. 2014;9:e92270.
5. Özüdoğru A, Gelecek N. Effects of closed and open kinetic chain exercises on pain, muscle strength, function, and quality of life in patients with knee osteoarthritis. Revista da Associação Médica Brasileira. 2023;69:e20230164.
6. Bennell KL, Hinman RS, Metcalf BR, et al. Relationship of knee joint proprioception to pain and disability in individuals with knee osteoarthritis. Journal of orthopaedic research. 2003;21:792–7.
7. Van der Esch M, Steultjens M, Harlaar J, Knol D, Lems W, Dekker J. Joint proprioception, muscle strength, and functional ability in patients with osteoarthritis of the knee. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2007;57:787–93.
8. Pai YC, Rymer WZ, Chang RW, Sharma L. Effect of age and osteoarthritis on knee proprioception. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1997;40:2260–5.
9. Ribeiro IC, Coimbra AMV, Costallat BL, Coimbra IB. Relationship between radiological severity and physical and mental health in elderly individuals with knee osteoarthritis. Arthritis Research & Therapy. 2020;22:1–7.
10. Mellemkjær FH, Madeleine P, Nørgaard JE, Jørgensen MG, Kristiansen M. Assessing Isometric Quadriceps and Hamstring Strength in Young Men and Women: Between-Session Reliability and Concurrent Validity. Applied Sciences. 2024;14:958.
11. Akaras E, Çobanoğlu G, Suner-keklik S, et al. Changes in Physical Fitness Parameters with Increasing Age. Research in Sport Education and Sciences. 2024;26:88–97.
12. Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. Clinical Orthopaedics and Related Research®. 2016;474:1886–93.
13. Tüzün E, Eker L, Aytar A, Daşkapan A, Bayramoğlu M. Acceptability, reliability, validity and responsiveness of the Turkish version of WOMAC osteoarthritis index. Osteoarthritis and cartilage. 2005;13:28–33.
14. Omori G, Koga Y, Tanaka M, et al. Quadriceps muscle strength and its relationship to radiographic knee osteoarthritis in Japanese elderly. Journal of orthopaedic science. 2013;18:536–42.
15. Patterson BE, Girdwood MA, West TJ, et al. Muscle strength and osteoarthritis of the knee: a systematic review and meta-analysis of longitudinal studies. Skeletal radiology. 2023;52:2085–97.
16. Al-Johani AH, Kachanathu SJ, Hafez AR, et al. Comparative study of hamstring and quadriceps strengthening treatments in the management of knee osteoarthritis. Journal of physical therapy science. 2014;26:817–20.
17. Purba TSP, Moeliono MA, Sastradimadja SB. Effect of quadriceps muscle strengthening exercise on quadriceps and hamstring muscle strength ratio in patients with osteoarthritis grade 2 and 3. International Journal of Integrated Health Sciences. 2017;5:64–9.
18. Aslan Ö, Batur EB, Meray J. The importance of functional hamstring/quadriceps ratios in knee osteoarthritis. Journal of sport rehabilitation. 2019;29:866–70.
19. Takagi S, Omori G, Koga H, et al. Quadriceps muscle weakness is related to increased risk of radiographic knee OA but not its progression in both women and men: the Matsudai Knee Osteoarthritis Survey. Knee Surgery, Sports Traumatology, Arthroscopy. 2018;26:2607–14.
20. Luc-Harkey BA, Safran-Norton CE, Mandl LA, Katz JN, Losina E. Associations among knee muscle strength, structural damage, and pain and mobility in individuals with osteoarthritis and symptomatic meniscal tear. BMC musculoskeletal disorders. 2018;19:1–11.
21. Sharma L, Pai Y-C. Impaired proprioception and osteoarthritis. Current opinion in rheumatology. 1997;9:253–8.
22. Knoop J, Steultjens M, Van der Leeden M, et al. Proprioception in knee osteoarthritis: a narrative review. Osteoarthritis and cartilage. 2011;19:381–8.
23. Mani E, Tüzün EH, Angın E, Eker L. Lower extremity proprioceptive sensation in patients with early stage knee osteoarthritis: a comparative study. The Knee. 2020;27:356–62.
24. de Oliveira DCS, Barboza SD, da Costa FD, Cabral MP, Silva VMP, Dionisio VC. Can pain influence the proprioception and the motor behavior in subjects with mild and moderate knee osteoarthritis? BMC musculoskeletal disorders. 2014;15:1–8.

25. Ramirez DS, van der Leeden M, Knol DL, et al. Association of postural control with muscle strength, proprioception, self-reported knee instability and activity limitations in patients with knee osteoarthritis. Journal of rehabilitation medicine. 2013;45:192–7.
26. Lee S-S, Kim H-J, Ye D, Lee D-H. Comparison of proprioception between osteoarthritic and age-matched unaffected knees: a systematic review and meta-analysis. Archives of Orthopaedic and Trauma Surgery. 2021;141:355–65.
27. Kim D, Park G, Kuo L-T, Park W. The effects of pain on quadriceps strength, joint proprioception and dynamic balance among women aged 65 to 75 years with knee osteoarthritis. BMC geriatrics. 2018;18:1–6.
28. Kwon SB, Ku Y, Han H-S, Lee MC, Kim HC, Ro DH. A machine learning-based diagnostic model associated with knee osteoarthritis severity. Scientific Reports. 2020;10:15743.
29. Wailoo A, Hernandez Alava M, Escobar Martinez A. Modelling the relationship between the WOMAC osteoarthritis index and EQ-5D. Health and quality of life outcomes. 2014;12:1–6.
30. Bellamy N, Wells G, Campbell J. Relationship between severity and clinical importance of symptoms in osteoarthritis. Clinical rheumatology. 1991;10:138–43.
31. Khalil NFW, El-sherif S, El Hamid MMA, Elnemr R, Taleb RSZ. Role of global femoral cartilage in assessing severity of primary knee osteoarthritis. Egyptian Rheumatology and Rehabilitation. 2022;49:16.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Clinicopathologic Evaluation of Borderline Ovarian Tumours: A Tertiary Centre Experience

Borderline Over Tümörlerinin Klinikopatolojik Değerlendirilmesi: Üçüncü Basamak Hastane Deneyimi

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ABSTRACT

Objective: *Borderline ovarian tumours (BOTs) are rare tumours in the intermediate category of benign and malignant ovarian neoplasms. This study presents the clinicopathological features of the cases diagnosed with BOT in the pathology department.*

Material and Methods: *The 139 patients were selected retrospectively. Haematoxylin&eosin slides were re-evaluated according to the 2020 World Health Organization classification. The data of the patients were obtained from the hospital archive.*

Results: *The mean age was 44.8. Intraoperative consultation was performed on 114 patients, and 86 of them (75.4%) were diagnosed with BOT. The most common histology was serous, followed by mucinous and seromucinous (54.8%, 32.5%, and 7.6%, respectively). Serous histology was observed in 16 of 18 bilateral BOT patients and mucinous histology was not seen. Mean tumour sizes were 10.4 cm in serous BOTs, 18.5 cm in mucinous BOTs and 12.4 cm in seromucinous BOTs. Mean CA-125 levels were 180.2 U/ml (N: 35 U/ml) in serous BOTs, 49.5 U/ml in mucinous BOTs and 35.4 U/ml in seromucinous BOTs. Mean CA-19.9 levels were 85.6 U/ml (N: 35 U/ml) in serous BOTs, 54.4 U/ml in mucinous BOTs and 93 U/ml in seromucinous BOTs. The recurrence rate was 10.9% (n=15), and no disease-related death was seen.*

Conclusions: *Serous BOT is the most common subtype, especially since most bilateral BOT has serous histology. Interestingly, the mean CA-19.9 level of seromucinous BOTs was higher than serous and mucinous BOTs. The prognosis can be excellent since the recurrence was observed in very few patients, and no disease-related death was detected.*

Key words: *borderline ovarian tumour; Brenner tumour; neoplasms, cystic, mucinous, and serous; ovarian neoplasms; recurrence*

ÖZET

Amaç: *Borderline over tümörleri (BOT), benign ve malign over neoplazmlarının ara kategorisinde yer alan, nadir sıklıkta görülen tümörlerdir. Bu çalışmada, patoloji bölümünde BOT tanısı alan olguların klinikopatolojik özelliklerinin sunulması amaçlanmıştır.*

Gereç ve Yöntem: *Patoloji bölümünde tanı alan 139 hasta retrospektif olarak seçildi. Vakaların hematoksilen&eozin boyalı lamları 2020 Dünya Sağlık Örgütü sınıflandırmasına göre yeniden değerlendirildi. Hastaların verileri hastane arşivinden elde edildi.*

Bulgular: *Ortalama yaş 44,8 idi. İntraoperatif konsültasyon yapılan 114 hastanın 86'sına (%75,4) BOT tanısı konuldu. En sık görülen histolojik alt tip serözdü, bunu müsinöz ve seromüsinöz takip ediyordu (%54,8, %32,5 ve %7,6). On sekiz bilateral BOT hastasının 16'sında seröz histoloji gözlendi; müsinöz histoloji görülmedi. Ortalama tümör boyutları seröz BOT'larda 10,4 cm, müsinöz BOT'larda 18,5 cm ve seromüsinöz BOT'larda 12,4 cm idi. Ortalama CA-125 düzeyleri seröz BOT'larda 180,2 U/ml (N: 35 U/ml), müsinöz BOT'larda 49,5 U/ml ve seromüsinöz BOT'larda 35,4 U/ml idi. Ortalama CA-19,9 düzeyleri seröz BOT'larda 85,6 U/ml (N: 35 U/ml), müsinöz BOT'larda 54,4 U/ml ve seromüsinöz BOT'larda 93 U/ml idi. Rekürrens oranı %10,9 idi (n=15) ve hastalığa bağlı ölüm görülmedi.*

Sonuç: *Seröz BOT en yaygın alt tipti ve özellikle bilateral BOT'ların büyük çoğunluğu seröz histolojiye sahipti. İlginç bir şekilde, seromüsinöz BOT'ların ortalama CA-19,9 seviyesi seröz ve müsinöz BOT'lardan daha yüksekti. Çok az hastada rekürrens gözlendiğinden ve hastalığa bağlı ölüm tespit edilmediğinden, prognozun mükemmel olduğu söylenebilir.*

Anahtar kelimeler: *borderline over tümörü; Brenner tümörü; neoplazmlar, kistik, müsinöz ve seröz; over neoplazmları; rekürrens*

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Introduction

Borderline ovarian tumour (BOT) is a neoplasm characterized by cellular proliferation with mild nuclear atypia but without stromal invasion[1]. It is classified as an intermediate between benign and malignant ovarian epithelial tumours. It has six subgroups distinguished by epithelial cell type, commonly comprising serous, mucinous, and less commonly endometrioid, clear cell, seromucinous, and Brenner BOT[2,3]. Compared with ovarian carcinoma, BOTs are portrayed clinically by a younger age at diagnosis and better overall survival[4,5]. BOTs can exist either unilaterally or bilaterally[6]. The majority of them belong to serous and mucinous subtypes[2,3]. Although it is stated that BOTs do not make stromal invasion, they can be associated with microinvasion, intraepithelial carcinoma, lymph node involvement, and peritoneal implants [1,7].

At diagnosis, most BOTs are stage I according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system. The main treatment is surgical same as for malignant ovarian tumours. Fertility-sparing surgery that preserves the uterus and at least part of one ovary is preferable for young women. Hysterectomy and bilateral salpingo-oophorectomy could be performed in people who have completed their fertility. Routine lymph node dissection is controversial because there is no difference in the recurrence or survival rate of whether lymphadenectomy is performed or not[8,9]. Follow-up with tumour markers such as CA-125, CEA and CA-19.9 could have a role in the postoperative period because of elevated in 25–60% of patients at diagnosis[10].

The study aims to retrospectively analyse the clinical and histopathological features of BOTs diagnosed in our centre and investigate their compatibility with the literature.

Material and Methods

Ethics committee approval was received for this study from the university's ethics committee (Approval date: 14/03/2021, number: 0110). Written informed consent was obtained from patients who participated in this study. We retrospectively examined the patients with BOT diagnosed in the pathology department between January 2006 and December 2017. The cases were reviewed by two pathologists (SDA and SY) on haematoxylin and eosin-stained slides and reclassified according to the 2020 World Health Organization (WHO) classification. The presence of epithelial proliferation <10% of the tumour and the invasion ≥5 mm in the greatest dimension in any single focus were accepted as exclusion criteria. Stromal microinvasion was defined as <5 mm invasion in the greatest dimension, and these cases were included in the study. In serous BOT cases, the implants were evaluated as non-invasive and invasive implants (low-grade serous carcinoma).

Statistical Analysis

From the hospital database, the patient's age, tumour side (right/left/bilateral), mean tumour size, the levels of pre-operative CA-125 (Cancer Antigen-125), CA-19.9 (Cancer Antigen-19.9), intraoperative consultation (frozen procedure) pathology records, type of surgical treatment, presence of implants, lymph node status, presence of recurrence and results of malignant transformation were noted. All data were collected with Microsoft Excel (Redmond, WA, USA).

Results

A total of 139 patients were included in the study. Clinicopathological parameters of all patients were given in Table 1. The mean age at diagnosis was 44.9 (range: 12–80). The mean age by histological type was 43.1, 45.3, and 45.3 years in serous, mucinous, and seromucinous BOTs, respectively. Forty-eight tumours (35.8%) were localized on the right side and 68 (50.7%) tumours were on the left side. Bilateral tumours were observed in 18 (13.4%) patients. The tumour localization of 5 patients could not be reached because they were consultation cases. The histologic types of BOTs according to localizations were given in Table 2. Patients with 18 bilateral tumours were added separately when calculating the mean tumour size and there was a total of 157 tumours. The tumour size of 13 patients could not be reached, therefore the tumour size of 144 tumours was calculated. The mean tumour size was 13.4 cm (range: 0.8–35). Of 129 patients whose preoperative CA-125 level was reached, 39 (30.2%) had high levels (≥35 U/ml). Of 126 patients whose CA-19.9 level was reached, 29 (23%) had high levels (≥35 U/ml). The comparison of the number of tumours, the mean age, the mean tumour size, and the levels of CA-125 and CA-19.9 at serous, mucinous and seromucinous BOTs were made in Table 3.

Intraoperative consultation was performed on 114 of 139 (82%) patients. The sensitivity of the frozen

Table 1. *Clinicopathological parameters of all patients*

	Number of patients (%)
Total number of patients	139
Mean age, years (range)	44.9 (12–80)
Mean tumour size, cm (range)	13.4 (0.8–35)
Laterality (n=134)	
– Right	48 (35.8%)
– Left	68 (50.7%)
– Bilateral	18 (13.4%)
Histologic type, per tumour (n=157)	
– Serous	68 (43.3%)
– Serous micropapillary/cribriform	10 (6.4%)
– Serous microinvasive	8 (5.1%)
– Mucinous	42 (26.8%)
– Mucinous + intraepithelial carcinoma	5 (3.2%)
– Mucinous microinvasive	4 (2.5%)
– Seromucinous	12 (7.6%)
– Brenner	2 (1.3%)
– Endometrioid microinvasive	3 (1.9%)
– Clear cell microinvasive	1 (0.6%)
– Serous + endometrioid	1 (0.6%)
– Seromucinous + endometrioid	1 (0.6%)
Frozen procedure results (n=114)	
– Benign	20 (17.5%)
– Borderline	86 (75.4%)
– Malignant	2 (1.8%)
– Could not be decided	6 (5.3%)
Stage (n=139)	
– IA	91 (65.5%)
– IB	7 (5%)
– IC	26 (18.7%)
– IIIA1	3 (2.2%)
– IIIB	1 (0.7%)
– IIIC	11 (7.9%)
Tumour implants (n=45)	
– Non-invasive	5 (11.1%)
– Invasive	3 (6.7%)
– Absence	37 (82.2%)
Lymph node involvement (n=48)	
– Presence	7 (14.6%)
– Absence	41 (85.4%)
Recurrence (n=137)	
– Presence	15 (10.9%)
– Absence	122 (89.1%)
Malignant transformation (n=137)	
– Presence	4 (2.9%)
– Absence	133 (97.1%)

Table 2. *The histologic types of borderline ovarian tumours according to primary localizations*

Tumour localizations	Histologic type	Number of patients (%)
Right	Serous	21 (43.6%)
	Serous micropapillary/cribriform	3 (6.3%)
	Serous microinvasive	1 (2.1%)
	Mucinous	17 (35.4%)
	Mucinous + intraepithelial carcinoma	2 (4.2%)
	Mucinous microinvasive	1 (2.1%)
	Seromucinous	2 (4.2%)
	Endometrioid microinvasive	1 (2.1%)
Total: 48 (100%)		
Left	Serous	23 (33.8%)
	Serous micropapillary/cribriform	3 (4.4%)
	Serous microinvasive	3 (4.4%)
	Mucinous	23 (33.8%)
	Mucinous + intraepithelial carcinoma	3 (4.4%)
	Mucinous microinvasive	2 (2.9%)
	Seromucinous	7 (10.3%)
	Brenner	2 (2.9%)
	Seromucinous + endometrioid	1 (1.5%)
	Clear cell microinvasive	1 (1.5%)
Total: 68 (100%)		
Bilateral (n=18)	Serous	11 (61.1%)
	Serous micropapillary/cribriform	1 (5.6%)
	Serous microinvasive (right side) + Serous micropapillary/cribriform (left side)	2 (11.1%)
	Serous microinvasive (right side) + Serous (left side)	1 (5.6%)
	Seromucinous	1 (5.6%)
	Serous + endometrioid (right side) + Serous (left side)	1 (5.6%)
	Endometrioid microinvasive	1 (5.6%)
Total: 18 (100%)		

procedure was 75.4%. It was determined that two of the patients who underwent the frozen procedure were overdiagnosed, and 20 of them were underdiagnosed. Of the 2 cases overdiagnosed in the frozen procedure, 1 was signed out as serous BOT and 1 as mucinous BOT on the permanent pathology report. Of the 20 cases underdiagnosed in the frozen procedure, 15 were signed out as mucinous BOT, 3 as serous, 1 as seromucinous BOT and 1 as Brenner BOT on the permanent pathology report. Immunohistochemical stainings

Table 3. *The comparison of the number of tumours, the mean age, the mean tumour size, and the levels of CA-125 (Cancer Antigen-125) and CA-19.9 (Cancer Antigen-19.9) at serous, mucinous and seromucinous borderline ovarian tumours*

	Serous (including micropapillary/ cribriform and microinvasive)	Mucinous (including intraepithelial carcinoma and microinvasive)	Seromucinous	All
Number of tumours (%)	86 (54.8%)	51 (32.5%)	12 (7.6%)	157 (100%)
Mean age, years	43.1	45.3	45.3	44.9
Mean tumour size, cm	10.4	18.5	12.4	13.4
Number of high CA-125 level/ number of tumours (%)	21/86 (24.4%)	14/51 (27.5%)	3/12 (25%)	39/157 (24.8%)
Mean CA-125 level, U/ml	180.2	49.5	35.4	128.6
Number of high CA-19.9 level/ number of tumours (%)	9/86 (10.5%)	15/51 (29.4%)	3/12 (25%)	29/157 (18.5%)
Mean CA-19.9 level	85.6	54.4	93	76.6

were applied to 6 of 51 cases diagnosed with mucinous BOT to differentiate primary/metastasis. Four cases were cytokeratin 7 positive and cytokeratin 20 negative, whereas 2 cases were cytokeratin 7 positive and cytokeratin 20 positive.

Fertility-sparing surgery was performed in 46 of 139 (33.1%) patients. Ten of these patients underwent staging surgery, and 10 underwent comprehensive staging surgery. Of the 93 (66.9%) patients who did not have fertility-sparing surgery, 47 had staging surgery, and 10 had comprehensive staging surgery. Appendectomy was performed in 33 patients. Two of the patients who underwent appendectomy were diagnosed with low-grade mucinous neoplasia, and the BOT in these two cases had a serous histologic type. Non-invasive tumour implants were diagnosed in 5 patients (11.1%) and invasive implants were diagnosed in 3 patients (6.7%) in serous BOTs cases. Disseminated peritoneal adenomucinosis was detected in 4 of 23 mucinous BOT cases for which omental/peritoneal sampling was performed. All patients were staged based on the FIGO staging system 2020. Of all 139 patients, 124 (89.2%) had FIGO stage I disease, and 15 (10.8%) had stage III disease.

The mean follow-up period was 75.3 months. Recurrence was observed in 15 patients during follow-up. Of these patients, 8 had serous BOT, 2 had serous micropapillary/cribriform BOT, 2 had mucinous BOT, 2 had seromucinous BOT, and 1 had seromucinous + endometrioid BOT. Of these patients who developed recurrence, 3 of them had a malignant transformation, and 1 had recurrent disease with borderline histology. Six patients died of other reasons, and none of the patients died of disease.

Discussion

Borderline ovarian tumours generally have a good prognosis between benign and malignant tumours. It occurs at a younger age than ovarian carcinoma and has a low stage at the time of diagnosis. In this study of 139 patients, we examined borderline ovarian tumours diagnosed in our department. The mean age was slightly higher than in previous studies and was 44.9 years, ranging from 12 to 80 years; 61 of these patients (43.9%) were <40 years. And the mean age was found to be 38 years and above in studies[8,9,11,12]. When we compared the mean age according to the histological types, it was seen that serous BOT occurred slightly younger than mucinous and seromucinous BOTs. In the literature, a major part of the cases with BOTs are serous and mucinous subtypes. Consistent with previous studies, the most common histological type in the present study was a serous type, followed by mucinous and seromucinous types, respectively[8,9,11,12].

Although BOT is known to generally proceed with a favourable prognosis, differentiating between benign and malignant lesions at diagnosis is also important for correct surgical treatment. Hence, the accurate diagnosis is based on histopathological examination, which highlights the matter of intraoperative consultation (frozen procedure). The diagnostic criteria of BOT require adequate sampling to determine 10% atypical proliferation features without invasion. In our study, 114 of 139 (82%) patients underwent the frozen procedure, and the accuracy rate was reported at 75.4%. In studies, the accuracy rates of BOT diagnosis in the frozen procedure range between 55.5% and 79%[13–17]. In the permanent pathology reports, a mucinous BOT diagnosis was given to 15 of 20 cases considered benign

in the frozen procedure. This result, which is not unexpected, is consistent with the literature[13]. Reasons such as less sampling, sampling errors and misinterpretation may lead to under or overdiagnosis[18,19]. Pathologists should pay attention to some details that might help to reduce the inconsistency of frozen procedures, such as understanding the histologic limitations of the frozen procedure and routing to permanent pathology diagnosis when needed.

In our study, the mean tumour size was slightly lower in the serous subtype compared to the mucinous and seromucinous subtypes. In addition, mucinous BOTs had a mean tumour size of 18.5 cm, higher than the mean size of all tumours (13.4 cm). In the study of Houck et al., the mean diameter of overall tumours was 13.7 cm, 10.2 cm for serous, and 20.1 cm for mucinous[15]. In the literature, a major part of the cases with BOTs are serous and mucinous subtypes. Consistent with previous studies in the present study, the most common histological type was a serous type, followed by mucinous and seromucinous types, respectively[8,9,11,12]. In a systematic review of 6362 cases, 78.9% of patients with BOT are diagnosed at FIGO stage I (20). In our study, 89.2% of our patients had stage I disease, which is more frequent than the literature. This result supports that patients with BOT have better survival than patients with ovarian cancer.

In our study, it was seen that high CA-125 levels were in 24.4% of serous BOTs, with a mean of 180.2 U/ml, 27.5% of mucinous BOTs, with a mean of 49.5 U/ml, 25% of seromucinous BOTs with a mean of 35.4 U/ml, while it was in 24.8% of all tumours with a mean of 128.6 U/ml. Although three studies, one from Türkiye, showed higher CA-125 levels in serous and mucinous BOTs than in our results, our mean CA-125 levels were slightly higher than the study of Gotlieb et al.[5,11,21]. In our patients with mucinous BOTs, CA-19.9 levels were more elevated than in patients with serous BOTs, and this result supports the other studies[21,22]. The mean CA-19.9 level was higher in seromucinous BOTs than in serous and mucinous BOTs. A case report was diagnosed as a seromucinous BOT derived from endometriosis due to the increase in CA-19.9 levels in the follow-up after the bilateral salpingo-oophorectomy because of peritoneal cysts[23]. It was reported that the CA-19.9 level decreased after the second operation.

In the present study, there were 10 patients with serous micropapillary/cribriform BOT, and one had bilaterality. Recurrence was observed in 2 of these 10 patients. The incidence of serous micropapillary/cribriform BOT was 6.4% in all tumours in our study and 11.6% in serous BOTs. Studies in the literature find different incidences, such as 1% and 25%[8,24]. Stromal microinvasion was defined as <5 mm invasion in the greatest dimension[25]. The effect of microinvasion on recurrence and prognosis is controversial in the literature. Studies indicate that microinvasion does not affect the patients' prognosis as few cases have been reported[5,26,27]. In this study, there were 8 patients with serous microinvasion BOT; none had a recurrence and/or malignant transformation.

The subclassification of extraovarian disease into invasive and non-invasive implants is one of the most important prognostic indicators for serous BOTs[28]. Invasive implants were considered a poor prognostic factor in the studies[29]. In our study, 11.1% of the patients had non-invasive implants, and 6.7% had invasive implants. Recurrence was observed in 2 of 3 patients with invasive implants. The histology of these two patients was serous BOT. Lymph node involvement is not considered an adverse prognostic factor[28–30]. However, one study reported worse progression-free survival in patients with paraaortic lymph node metastases in univariate analysis[31]. Our study observed lymph node involvement in 7 of 48 patients who underwent lymphadenectomy. Recurrence was observed in only 2 of these patients. In addition, the recurrence rate was between 2.7% and 16.6% in studies from Türkiye, and in our study, the recurrence rates were found to be 10.9%, consistent with the literature[5,8,9]. There were limitations in our study. It was a retrospective study without randomized designs and had some deficits in hospital records.

Conclusion

In conclusion, we presented the study of 139 patients with borderline ovarian tumours, and no disease-related death was found. The recurrence rate was found to be low; therefore, we can say that BOTs have an excellent prognosis. This is a publication in a tertiary hospital with pathologists specialising in gynecological pathology, with a high number of cases, and detailed clinical data contributing to the literature, making this study considerable.

References

1. Hauptmann S, Friedrich K, Redline R, Avril S. Ovarian borderline tumors in the 2014 WHO classification: evolving concepts and diagnostic criteria. Virchows Arch. 2017;(470):125–42.
2. Silverberg SG, Bell DA, Kurman RJ, Seidman JD, Prat J, Ath F, et al. Borderline Ovarian Tumors: Key Points and Workshop Summary. Hum Pathol. 2004;(35):910–7.
3. Seidman JD, Soslow RA, Vang R, Berman JJ, Stoler MH, Sherman ME, et al. Borderline Ovarian Tumors: Diverse Contemporary Viewpoints on Terminology and Diagnostic Criteria With Illustrative Images. Hum Pathol. 2004;(35):918–33.
4. Morice P, Uzan C, Fauvet R, Gouy S, Duvillard P, Darai E. Borderline ovarian tumour: pathological diagnostic dilemma and risk factors for invasive or lethal recurrence. Lancet Oncol. 2012;13:18–21.
5. Ayhan A, Seda E, Guven G, Guven S, Kucukali T. Recurrence and prognostic factors in borderline ovarian tumors. Gynecol Oncol. 2005;98:439–45.
6. Hannibal CG, Vang R, Junge J, Frederiksen K, Kurman RJ, Kjaer SK. A nationwide study of ovarian serous borderline tumors in Denmark 1978–2002. Risk of recurrence, and development of ovarian serous carcinoma. Gynecol Oncol [Internet]. 2016;(144):174–80. Available from:
7. Malpica A, Longacre TA. Prognostic indicators in ovarian serous borderline tumours. Pathology. 2017;1–9.
8. Gungor T, Cetinkaya N, Yalcin H, Ozdal B, Ozgu E, Baser E, et al. Retrospective evaluation of borderline ovarian tumors: single center experience of 183 cases. Arch Gynecol Obs. 2015;(291):123–30.
9. Birge O, Bakır MS, Karadag C, Dinc C, Doğan S, Tuncer HA, et al. Risk factors that increase recurrence in borderline ovarian cancers. Am J Transl Res. 2021;13(7):8438–49.
10. Poncelet C, Fauvet R, Yazbeck C, Coutant C, Darai E. Impact of serum tumor marker determination on the management of women with borderline ovarian tumors: Multivariate analysis of a French multicentre study. Eur J Surg Oncol [Internet]. 2010;36(11):1066–72. Available from:
11. Gotlieb WH, Chetrit A, Menczer J, Hirsh-Yechezkel G, Lubin F, Friedman E, et al. Demographic and genetic characteristics of patients with borderline ovarian tumors as compared to early stage invasive ovarian cancer. Gynecol Oncol. 2005;97(3):780–3.
12. Romagnolo C, Gadducci A, Sartori E, Zola P, Maggino T. Management of borderline ovarian tumors: Results of an Italian multicenter study. Gynecol Oncol. 2006;101(2):255–60.
13. Ferrero S, Morotti M, Venturini PL, Peñuela L, Vellone VG, Barra F. Accuracy of intra-operative frozen section in the diagnosis of borderline ovarian tumors and clinical impact of underdiagnosis. 2018;1(2):1–7.
14. Song T, Choi CH, Kim H, Kim MK, Kim T, Lee J, et al. Accuracy of frozen section diagnosis of borderline ovarian tumors. Gynecol Oncol [Internet]. 2011;122(1):127–31. Available from:
15. Houck K, Nikrui N, Duska L, Chang Y, Fuller AF, Bell D, et al. Borderline Tumors of the Ovary: Correlation of Frozen and Permanent Histopathologic Diagnosis. Obstet Gynecol. 2000;95(6):839–43.
16. Kim JH, Kim TJ, Park YG, Lee SH, Lee CW, Song MJ, et al. Clinical analysis of intra-operative frozen section proven borderline tumors of the ovary. J Gynecol Oncol. 2009;20(3):176–80.
17. Göl M, Baloglu A, Yigit S, Dogan M, Aydin Q, Yensel U. Accuracy of frozen section diagnosis in ovarian tumors: Is there a change in the course of time? Int J Gynecol Cancer. 2003;13(5):593–7.
18. Basaran D, Salman MC, Calis P, Ozek A, Ozgul N, Usubütün A, et al. Diagnostic accuracy of intraoperative consultation (frozen section) in borderline ovarian tumours and factors associated with misdiagnosis. J Obs Gynaecol. 2014;34(5):429–34.
19. Zaiem F, Deirawan H, Kherallah R, Fehmi O, Jang H, Kim S, et al. Accuracy and Reproducibility of Frozen Section Diagnosis in Ovarian Tumors: A 10-Year Experience at a Tertiary Cancer Center. Arch Pathol Lab Med. 2021;Aug 17.
20. du Bois AD, Ewald-Riegler N, Du Bois O, Harter P. Borderline tumors of the ovary-a systematic review. Geburtshilfe Frauenheilkd. 2009;69(9):807–33.
21. Song T, Lee H, Jung W, Yun S, Seong SJ, Choi CH, et al. Elevated Preoperative CA125 or CA19–9 in Borderline Ovarian Tumors: Could It Be Suggestive of Advanced Stage or a Poor Prognosis ? Gynecol Obstet Invest. 2017;83(1):45–51.
22. Engelen MJA, Bruijn HWA De, Hollema H, ten Hoor KA, Willemse PHB, Aalders JG, et al. Serum CA 125, Carcinoembryonic Antigen, and CA 19–9 as Tumor Markers in Borderline Ovarian Tumors. Gynecol Oncol. 2000;78(1):16–20.
23. Yamada T, Eguchi S, Yokoo I, Arimoto T. Occurrence of seromucinous borderline tumours in the peritoneal lesions after bilateral salpingo-oophorectomy. BMJ Case Rep. 2020;13(12):e234692.
24. Park J, Kim D, Kim J, Kim Y, Kim K, Kim Y, et al. Micropapillary pattern in serous borderline ovarian tumors: Does it matter ? Gynecol Oncol [Internet]. 2011;123(3):511–6. Available from:
25. WHO Classification of Tumours Female Genital Tumours 5th Edition. Lyon (France) : International Agency for Research on Cancer;2020. 40 p.
26. Buttin BM, Herzog TJ, Powell MA, Rader JS, Mutch DG. Epithelial Ovarian Tumors of Low Malignant Potential: The Role of Microinvasion. Obs Gynecol. 2002;99(1):11–7.
27. Morris RT, Gershenson DM, Silva EG, Follen M, Morris M, Wharton JT. Outcome and Reproductive Function After Conservative Surgery for Borderline Ovarian Tumors. Obs Gynecol. 2000;95(4):541–7.
28. JD S, RJ K. Ovarian serous borderline tumors: a critical review of the literature with emphasis on prognostic indicators. Hum Pathol. 2000;31(5):539–57.
29. Qian X, Hua X, Wu J, Shen Y, Cheng X, Wan X. Clinical Predictors of Recurrence and Prognostic Value of Lymph Node Involvement in the Serous Borderline Ovarian Tumor. Int J Gynecol Cancer. 2017;00(00):1–6.
30. McKenney JK, Balzer BL, Longacre TA. Lymph node involvement in ovarian serous tumors of low malignant potential (borderline tumors) : pathology, prognosis, and proposed classification. Am J Surg Pathol. 2006;30(5):614–24.
31. Ureyen I, Karalok A, Tasci T, Turkmen O, Boran N, Tulunay G, et al. The Factors Predicting Recurrence in Patients With Serous Borderline Ovarian Tumor. Int J Gynecol Cancer. 2016;26(1):66–72.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Investigation of Viral and Bacterial Agents in Samples Taken from Patients with Suspected Upper Respiratory Tract Infection

Üst Solunum Yolu Enfeksiyonu Şüphesi Olan Hastalardan Alınan Örneklerde Viral ve Bakteriyel Etkenlerin Araştırılması

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ABSTRACT

Aim: *Upper respiratory tract infection (URTI) complaints are the most common causes of admission to outpatient clinics and rapid detection by Multiplex-PCR method contributes to the monitoring and control of infection by easily evaluating the etiology of viral and bacterial agents regionally. This study aimed to evaluate the etiology of pathogens with a 24-X viral and bacterial respiratory Multiplex-PCR panel in patients admitted to Kafkas University Health Research and Application Hospital with URTI symptoms between November 2023 and February 2024.*

Materials and Methods: *The presence of viral and bacterial pathogens was analyzed by Multiplex-PCR method in nasopharyngeal swab samples obtained from 100 patients diagnosed with URTI by physical examination such as allergic rhinitis and acute bronchitis. The respiratory panel contained 24 different microorganisms such as SARS CoV-2, Influenza-A/B, Human Rhinovirus/Enterovirus, Human Metapneumovirus, Respiratory Syncytial Virus A/B, Human Parainfluenza Virus-1/2/3/4, Human Coronavirus 229E/OC43/NL63/HKU1, Human Parechovirus, Adenovirus, Human Bocavirus, Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila and Bordotella pertussis.*

Results: *According to the findings, the highest number of applications was in January. Out of 100 patients, 73% (n=73) were positive and 27% (n=27) were negative, the most common viral agent was INF A (n=33, 26.9%) while the most common bacterial agent was S.pneumoniae (n=19, 15.4%). Of 73 positive patients, 38.3% (n=28) had co-infections, 11% (n=8) had only bacterial agents, and 50.7% (n=37) had viral agents.*

Conclusions: *In conclusion, URTI agents were rapidly detected by Multiplex-PCR and their incidence was investigated in this study. Finally, it aims to prevent possible epidemics, unnecessary antibiotic use, mortality and morbidity and to contribute to other academic studies with rapid diagnosis and treatment of URTI infections.*

Key words: *URTI; SARS-CoV-2; influenza; multiplex PCR*

ÖZET

Amaç: *Üst solunum yolu enfeksiyonu (ÜSYE) şikâyetleri polikliniklere en sık başvuru nedenidir. ve Multiplex-PCR yöntemi ile hızlı tespit, viral ve bakteriyel etkenlerin etiyolojisini bölgesel olarak kolayca değerlendirerek enfeksiyonun izlenmesine ve kontrolüne katkı sağlamak oldukça önem arz etmektedir. Bu çalışmanın amacı, Kasım 2023-Şubat 2024 tarihleri arasında Kafkas Üniversitesi Sağlık Araştırma ve Uygulama Hastanesine ÜSYE semptomları ile başvuran hastalarda 24-X viral ve bakteriyel Solunum Yolu Multiplex-PCR paneli ile patojenlerin etiyolojisini değerlendirmektir.*

Gereç ve Yöntem: *Alerjik rinit ve akut bronşit gibi ÜSYE ön tanısı konulan 100 hastadan alınan nazofarengeal sürüntü örneklerinde viral ve bakteriyel patojenlerin varlığı Multiplex-PCR yöntemi ile analiz edilmiştir. Solunum paneli SARS CoV-2, Influenza-A/B, Human Rhinovirus/Enterovirus, Human Metapneumovirus, Respiratory Syncytial Virus A/B, Human Parainfluenza Virus-1/2/3/4, İnsan Coronavirus 229E/OC43/NL63/HKU1, İnsan Parechovirus, Adenovirus, İnsan Bocavirus, Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila ve Bordotella pertussis gibi 24 farklı mikroorganizma içermekteydi.*

Bulgular: *En yüksek başvuru sayısı ocak ayında gerçekleşmiştir. Yüz hastanın %73'ü (n=73) pozitif, %27'si (n=27) negatif olup, en sık görülen viral etken INF A (n=33, %26,9), en sık görülen bakteriyel etken ise S. pneumoniae (n=19, %15,4) olarak raporlanmıştır. Pozitif 73 hastanın %38,3'ünde (n=28) en az iki ajanın etken olduğu ko-enfeksiyon mevcuttu.*

Sonuç: *Bu çalışmada ÜSYE etkenleri Multiplex-PCR ile hızlı bir şekilde tespit edilmiş ve görülme sıklıkları araştırılmıştır. Sonuç olarak, ÜSYE enfeksiyonlarının hızlı tanı ve tedavisi ile olası salgınların, gereksiz antibiyotik kullanımının, mortalite ve morbiditenin önlenmesi ve diğer akademik çalışmalara katkı sağlanması amaçlanmıştır.*

Anahtar kelimeler: *ÜSYE; SARS-CoV-2; influenza; multiplex PCR*

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Introduction

The human respiratory system consists of the upper respiratory tract (URT) and lower respiratory tract, harboring a diverse microbial community. The URT includes the nose, mouth, sinuses, pharynx and larynx[1]. Upper respiratory tract infection (URT) ranks first among diseases that affect the economy, resulting in a loss of workforce and treatment costs. If not treated appropriately, it can cause serious complications and sequelae[2]. Viral and bacterial agents generally cause respiratory tract infections (RTIs), and both have similar symptoms, including fever, dry cough and sore throat[3]. These infections can manifest as otitis media, pharyngitis, laryngitis, rhinitis, and nasopharyngitis. Additionally, URTs can commonly be detected during the winter season[4], pediatric patients constitute 44% of the total number of patients admitted to hospitals with URTI, and 21% were prescribed antibiotics[1].

It is known that avian and swine-origin Influenza A viruses, animal reservoir-independent Influenza B viruses, Respiratory Syncytial Virus (RSV), Human Parainfluenza viruses, Human Metapneumovirus, Human Parechovirus, Human Rhinovirus, Human Bocavirus, Adenoviruses, Human Coronaviruses, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Chlamydophila pneumoniae* are circulating as bacterial and viral agents for URTIs in our country. These pathogens are primarily detected between October and April and can also be circulating from spring through winter[5–8]. The disease occurs nearly 2–4 and 6–10 times in a season in adults and children, respectively. The transmission typically occurs through three primary routes: direct and indirect contact, aerosol transmission, and droplet transmission[6,9,10]. For any infectious disease, including RTIs, the most suitable diagnostic methods are those based on rapid and accurate nucleic acid molecular diagnostic techniques such as Polymerase Chain Reaction (PCR), which rely on fully automated and integrated molecular diagnostic systems that are cost– and time-efficient, while also ensuring sensitivity and accuracy[3]. The Multiplex PCR technique should be used to determine multiple agents, especially in RTIs.

This study aimed to evaluate the etiology of pathogens with a 24-X viral and bacterial respiratory Multiplex-PCR panel in patients admitted to Kafkas University Health Research and Application Hospital with URTI symptoms between November 2023 and February 2024.

Material and Methods

A total of 100 patients aged 18–65 years who admitted to the outpatient clinics and emergency departments of Kafkas University Health Research and Application Hospital between November 2023 and February 2024 and who had at least one of the clinical symptoms of acute bronchitis, pneumonia, pain, cough, or acute upper respiratory tract infections, were included in the study. Nasopharyngeal swab samples were previously collected for routine analysis in the Medical Microbiology Laboratory. The samples were stored at -80°C until the experimental day, and then they were used for multiplex PCR analysis targeting 24 viral and bacterial respiratory pathogens. Clinical data, including the admission department, gender, age, and medical history of the patients, were obtained from the hospital archive and recorded. After a laboratory technician collected the nasopharyngeal swab samples, they were immediately placed in vNAT® transfer tubes, then numbered and sent to the laboratory on the same day. Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the Faculty of Medicine, Kafkas University (Date: 26.04.2023, Decision No: 212).

The Bio-speedy Extraction kit (Bioeksen, Türkiye), based on the magnetic bead method, was used according to the manufacturer's instructions for nucleic acid extraction from the nasopharyngeal swab samples. The extraction was performed using the Zybio EXM 3000 device (Bioeksen, Türkiye). The respiratory tract RT-qPCR MX-24L panel (Bioeksen, Türkiye) included 18 viral and 6 bacterial pathogens: Sars-CoV-2, EV/HRV, HPeV, HPiV (1/2/3/4), AdV, HBoV, HMPV, INF A/B, HCoV (OC43, HKU1, 229E, NL63), RSV A/B, S. pneumoniae, *Haemophilus influenzae*, *Bordetella pertussis*, *M.pneumoniae*, *C.pneumoniae*, and *Legionella pneumophila*. The "SY-1 Rxn and SY-2 Rxn" strips were placed on a cooling block at -22°C, and 10 µl of "template nucleic acid" patient samples were pipetted into each. The strips were carefully sealed and placed in the Micro-PCR (BMS Mic qPCR cycler, Bioeksen, Türkiye). The amplification curves were examined for each reaction well to determine the Cq values. Sigmoidal curves above the threshold value were interpreted as "positive," while non-sigmoidal curves were considered"negative."

Statistical analysis of the data was performed using IBM Statistical Package for Social Sciences (SPSS) program software version 22. Pearson's Chi-square test

was used to compare categorical data between groups. One-way ANOVA-Duncan's test should be used if the data showed normal distribution; so, the Mann-Whitney U test was applied for continuous data that did not show a normal distribution. Data were considered significant at $p<0.05$.

Results

Among the 100 patients studied, 47% were male, and 53% were female, with a mean age of 47.74±18.89 years. No statistically significant differences were detected between groups in terms of age and gender (Chi-square test, p=0.823). Of the patients, 73 (73%) were positive for one or more viral and bacterial pathogens, while 27 (27%) were negative. Co-infections were observed in 28 (38.3%) of 100 patients. The most frequently detected co-infections were INF A/B – *S.pneumoniae* (n=5, 18.6%) and SARS-CoV-2/ *S.pneumoniae* (n=3, 11.1%). The pathogens involved in co-infections and their numerical distribution are shown in Table 1.

A total of 73 patients were diagnosed as positive, 37 (50.7%) were caused solely by viral agents, while 8 (10.9%) were caused by bacterial agents. SARS-CoV-2 (n=14, 11.4%) and INF A/B (n=33, 26.8%) were the most frequently detected viral agents. On the other hand, *S.pneumoniae* (n=19, 15.5%) was the most commonly identified bacterial pathogen. The numerical distribution of the other detected pathogens by month is shown in Table 2.

Discussion

The respiratory system is a complex structure divided into the upper and lower respiratory tracts. If the microbiome of the URT, which has a high bacterial load, becomes imbalanced, the invasion of opportunistic pathogens can lead to serious infections[1,11]. The innate immune system is the first defense against these invading pathogens[12]. Viral upper respiratory infections include viral pharyngitis, sinusitis, otitis media, and viral rhinitis[13].

Respiratory infections affect vulnerable populations, such as pregnant women, infants, and the elderly,

Table 1. *Pathogens involved in co-infections and their distribution*

Co-Infection Pathogens		N	%
INF A/B	S.pneumoniae	6	21.4 %
SARS-CoV-2	S.pneumoniae	3	10.7 %
HRV / EV	H.influenzae	2	7.2 %
SARS-CoV-2	AdV	1	3.5 %
SARS-CoV-2	HPiV 3	1	3.5 %
INF A/B	RSV A/B, L.pneumophila, HPiV 2, H.influenzae, HBoV, HRV/EV	1	3.5 %
INF A/B	S.pneumoniae HPiV4	1	3.5 %
INF A/B	H.influenzae	1	3.5 %
INF A/B	B.pertussis	1	3.5 %
HRV / EV	C.pneumoniae, L.pneumophila, HPeV	1	3.5 %
HRV / EV	HBoV, RSV A/B, S.pneumoniae, C.pneumoniae	1	3.5 %
HRV / EV	S.pneumoniae, RSV A/B	1	3.5 %
AdV	H.influenzae	1	3.5 %
RSV A/B	HCoV-OC43	1	3.5 %
RSV A/B	S.pneumoniae, HPiV 4	1	3.5 %
HCoV-HKU1	H.influenzae, S.pneumoniae	1	3.5 %
HCoV-HKU1	HCoV-NL63, M.pneumoniae HCoV-OC43 RSV A/B	1	3.5 %
HCoV-HKU1	HPiV2, HCoV-229E, HCoV-OC43, HRV/EV	1	3.5 %
HCoV-229E	HPiV4	1	3.5 %
HCoV-HKU1	HCoV-OC43, HCoV-NL63, HPiV3, INF A, AdV	1	3.5 %
Total Number of Patients with Co-infection		28	100 %

Table 2. *Distribution of detected pathogens by month*

Monthly Distribution of Detected Pathogens																	
Year	2023								2024								
Months	November				December				January				February				
Weeks	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	TOTAL
SARS-CoV-2		1				3		1	1	2	1	2		1		2	14
INF A/B								1	5	7	6	11	1		1	1	33
HRV/EV									1		2	1	1	1	2		8
HMPV																	-
RSV A/B										3		3		1	2		9
HPIV-1																	-
HPIV-2													1				1
HPIV-3						1						1			1		3
HPIV-4										2						1	3
HCoV-229E													1			1	2
HCoV-OC43												1	1				2
HCoV-NL63												2					2
HCoV-HKU1											1	3	1				5
HPeV											1						1
AdV								1	1		1	1					4
HBoV														1	1		2
S. pneumoniae		1						2	1	4	4	3		2	1	1	19
H. influenzae									1	1	3	2			1		8
C. pneumoniae											1			1			2
B. pertussis									1			1					2
M. pneumoniae												1					1
L. pneumophila											1				1		2
Total	-	2	-	-	-	4	-	5	11	19	21	32	6	7	10	6	123

and are the most common seasonal infectious diseases worldwide, often leading to epidemics and pandemics[14]. Common respiratory viruses, such as HRVs, can cause milder infections, while SARS-CoV-2 and seasonal Influenza A/B viruses can lead to more serious or even fatal illnesses in at-risk populations[15–17]. Because the specific clinical symptoms of URIs are often minimal, it is difficult to diagnose viral and bacterial infections based on clinical signs and radiological findings[18]. Approximately 60–80% of URIs are viral, with the most frequently detected viruses being INF A/B, HRVs, RSV, HCoVs, and HPiVs. Similar reports can be seen in current studies conducted in our country and worldwide. Talay et al. reported that 82 (95.3%) and 4 (4.6%) of all patients were viral and bacterial, respectively, while Aydin et al. reported these rates as 60.4% and 39.4% for viral and bacterial agents, respectively[19,20]. A study conducted between 2009 and 2019 in China showed that viral positivity was detected as 46.9% and bacterial was 30.9% in children under 5-years. Additionally, Kwiyolecha et al. reported that 46.9% and 40.4% of all participants were positive regarding viral and bacterial pathogens, respectively. Like others, a Shenzhen Children's Hospital study found that 49.1% had either a single bacterial or viral pathogen among 273 positive cases[21–23]. Our study observed that 73.9% of patients had only viral infections, while 26.1% had only bacterial infections. Based on our findings and the current literature, it is seen that viral pathogens are the major cause of URIs when compared to bacterial pathogens and have maintained their activity over time.

In studies from Türkiye, the most commonly detected viral and bacterial pathogens were respectively HRV (23.3%), *S.pneumoniae* (18.6%), and HCoVs

(17.4%). A study reported the most commonly seen agents in URTIs as follows; *H.influenzae* (48.8%), *S.pneumoniae* (29.3%), RSV (23.3%), and AdV (19.1%), while another study was reported as follows; RSV (40.7%), and AdV (23.26%)[18,19,24]. Similar studies are available in current literature that show the most commonly detected viral and bacterial agents. The detected agents in our country were generally INF A, SARS-CoV-2, HCoV, HRV/EV, RSV A/B, *S.pneumoniae*, and *H.influenza* [25,26]. The viral and bacterial agents were nearly same (INF A/B, RSV, HCoV, HRV, and *S.pneumoniae*) in other countries such as China, Mexico, Tanzania[21,22,27,28].

In our study, we detected INF A (26.2%), SARS-CoV-2 (11.1%), RSV (7.14%), *H. influenzae* (7.14%), and *S.pneumoniae* (15.9%) as the most common pathogens. Our findings were consistent with other studies both globally and in Türkiye. When comparing our data with the literature, we can conclude that the circulation and prevalence of respiratory pathogens fluctuate over time.

Co-infection of respiratory viruses and bacteria contributes to disease severity[29]. INF A/B infections are generally associated with severe immunopathology in immunocompromised individuals, infants, and elderly patients, leading to secondary viral or bacterial co-infections and lower respiratory tract infections[16]. SARS-CoV-2 can also cause co-infections with bacteria or viruses by damaging respiratory epithelial surfaces, leading to inflammatory and immune dysregulation. A meta-analysis emphasized the role of co-infections and superinfections in SARS-CoV-2 patients. Thus, viral and bacterial co-infections are thought to worsen the clinical presentation of COVID-19, including in children[17,30]. Girgin's study found viral co-infections in 23.5% of 413 patients and triple viral co-infections in 11 cases, with co-infection rates for RSV/HRV, HRV/HPiV, HRV/EV, and HRV/HBoV being 21%, 10.5%, 11.6%, and 12.8%, respectively[2]. Kuşkucu et al. identified multiple pathogens in 408 samples, with the following agents; HCoV/RSV, HMPV/AdV, HPiV/EV, and HBoV (7.23%, 6.47%, 0.63%, and 0.13%, respectively)[14]. Şirin et al. found co-infection rates of 10.8% (n=13) in 120 patients, with the highest co-infection rate for HRV and *S.pneumoniae* (23.1%), followed by HRV and HCoV-229E (15.4%)[18]. Additionally, Aydin et al. found that 72.7% (n=144) of children had multiple pathogens combined with SARS-CoV-2 and *H.influenzae* (14%)[20]. These studies indicate that co-infection rates should not be overlooked. In our study, we found that 37% (n=27) of patients had co-infections, with the most common combinations as INF A – *S.pneumoniae* (18.5%), SARS-CoV-2 – *S.pneumoniae* (11.1%), and HRV/EV – H. influenzae (7.4%).

In conclusion, the prevalence of respiratory pathogens observed in our study is consistent with findings from both national and international researches. Our goal in identifying the viral and bacterial agents responsible for URIs was to provide etiological data and contribute to understanding which pathogens are circulating and causing infections. High-sensitivity and specificity tests like Multiplex-PCR are crucial for providing quick diagnoses, which can help in the rapid administration of antiviral treatments and the prevention of unnecessary antibiotic use, thus reducing the development of antibiotic resistance. These methods are essential for preventing pandemics and epidemics and reducing the economic and social burden of these infections. Therefore, we recommend that PCR-based diagnostic methods, such as Multiplex-PCR, be used effectively and widely in hospitals to improve health system efficiency, reduce healthcare costs, and facilitate the management of respiratory infections.

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References

1. Quinn-Bohmann N, Freixas-Coutin JA, Seo J, Simmons R, Diener C, Gibbons SM. Meta-analysis of the human upper respiratory tract microbiome reveals robust taxonomic associations with health and disease. BMC Biol. 2024;22:1–14.
2. Girgin HC. Çocuk hastalıkları servisine solunum yolu enfeksiyonu ile yatan hastalarda solunum virüs epidemiyolojisi ve klinik özellikleri [Doktora Tezi]. Dokuz Eylül Üniversitesi;İzmir, Türkiye, 2022.
3. Ma L, Zhu H, Jiang Y, Kong X, Gao P, Liu Y, et al. Development of a novel multiplex PCR method for the rapid detection of SARS-CoV-2, influenza A virus, and influenza B virus. Int J Anal Chem. 2024:4950391.
4. Thomas M, Bomar PA. Upper Respiratory Tract Infection. StatPearls. Treasure Island (FL). 2024.
5. Büyükşahin HN, Özçelik U. Acute bronchiolitis. Ankara EAH Tıp Derg. 2022;54(3):479–486.
6. Yildiz GN, Tukenmez G, Topaloglu I, Celebi O, Karamese M. Retrospective Evaluation of the Frequency of Respiratory Pathogens in Patients Admitted to Kafkas University Medical Faculty Hospital. Dicle Med J. 2024;51(4):539–546.
7. Parrott GL, Kinjo T, Fujita J. A compendium for Mycoplasma pneumoniae. Front Microbiol. 2016;7:513.
8. Dion CF, Ashurst JV. Streptococcus pneumoniae. StatPearls. Treasure Island (FL). 2024.
9. Dereköy S, Güçlü O. Upper respiratory tract infections. Klinik Tıp Aile Hekimliği. 2016;8(4):33–43.
10. Young JH, Jung BK, Kim JK. Epidemiological characterization of respiratory pathogens using the multiplex PCR FilmArray™ Respiratory Panel. Diagnostics. 2024;14(7):734.
11. Yuksel H, Turkel A. New Viral Pathogens among Pediatric Patients with Pneumonia. Güncel Göğüs Hastalıkları Serisi. 2014;2(1):106–116.
12. Man WH, de Steenhuijsen Piters WA, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. Nat Rev Microbiol. 2017;15(5):259–70.
13. Bellato M, Cappellato M, Longhin F, Del Vecchio C, Brancaccio G, Cattelan AM, et al. Uncover a microbiota signature of upper respiratory tract in patients with SARS-CoV-2. Sci Rep. 2023;13(1):16867.
14. Kuşkucu MA, Mete B, Tabak F, Midilli K. Prevalence and Seasonal Distribution of Respiratory Viruses in Adults Between 2010–2018. Turk Mikrobiyol Cem Derg. 2020;50(1):21–6.
15. Essaidi-Laziosi M, Alvarez C, Puhach O, Sattonnet-Roche P, Torriani G, Tapparel C, et al. Sequential infections with rhinovirus and influenza modulate the replicative capacity of SARS-CoV-2 in the upper respiratory tract. Emerging Microbes Infect. 2022;11(1):413–24.
16. Mifsud EJ, Kuba M, Barr IG. Innate immune responses to influenza virus infections in the upper respiratory tract. Viruses. 2021;13(10):2090.
17. Bell J, Chua A, Eccles R, Salvi S, Schellack N, Wang DY. Early intervention in acute upper respiratory tract infections. S Afr Pharm J. 2022;89(5):30–3.
18. Şahin MC. Investıgatıon of the Prevalence of Viral and Bacterial Agents by Multiplex PCR Method in Patients with a Pre-Diagnosis of Acute Respiratory Tract Infection in Isparta Province. Med J SDU. 2022;29(2):171–8.
19. Talay MN, Özer E. Investigation of Pathogen Distribution by Direct and Indirect Immunofluorescence Microscopy in Patients followed up with a Pre-Diagnosis of Atypical Pneumonia in a Pediatric Intensive Care Unit. Dicle Med J. 2022;49(3):513–20.
20. Aydın NN, Köse O, Aydın M, Kerget F, İba Yılmaz S. Epidemiology and Seasonal Distribution of Respiatory Viral Agents in the Pre-COVID-19 Period in Adults. Kırıkkale Üniv Tıp Fak Derg. 2022;24(3):496–500.
21. Kwiyolecha E, Groendahl B, Okamo B, Kayange N, Manyama F, Kidenya BR, et al. Patterns of viral pathogens causing upper respiratory tract infections among symptomatic children in Mwanza, Tanzania. Sci Rep. 2020;10(1):18490.
22. Li ZJ, Zhang HY, Ren LL, Lu QB, Ren X, Zhang CH, et al. Etiological and epidemiological features of acute respiratory infections in China. Nat Commun. 2021;12(1):5026.
23. Wang H, Li X, Zheng Y, Verhagen LM, Gu J, Li L, et al. Concordance in pathogen identification at the upper and lower respiratory tract of children with severe pneumonia. BMC Infect Dis. 2023;23:1–8.
24. Aydın E, Güney Yılmaz G, Aydın N, Dicle Y, Renders DP. Distribution of Respiratory Pathogens After the COVID-19 Pandemic: A Single-Center Pediatric Study From Türkiye. Kafkas J Med Sci. 2023;13(3):321–328.
25. Tekinsoy M. Çocukluk çağında üst solunum yolu enfeksiyonu etkeni virüslerin retrospektif olarak araştırılması [Uzmanlık Tezi]. Bursa Uludağ Üniversitesi;Bursa, Türkiye, 2022.
26. Karabulut N, Alacam S, Sen E, Karabey M, Yakut N. The epidemiological features and pathogen spectrum of respiratory tract infections, Istanbul, Turkiye, from 2021 to 2023. Diagnostics. 2024;14(11).
27. Bell C, Goss M, Norton D, Barlow S, Temte E, He C, et al. Descriptive epidemiology of pathogens associated with acute respiratory infection in a community-based study of K-12 school children (2015–2023). Pathogens. 2024;13(4).
28. Nieto-Rivera B, Saldana-Ahuactzi Z, Parra-Ortega I, Flores-Alanis A, Carbajal-Franco E, Cruz-Rangel A, et al. Frequency of respiratory virus-associated infection among children and adolescents from a tertiary-care hospital in Mexico City. Sci Rep. 2023;13(1):19763.
29. Manna S, McAuley J, Jacobson J, Nguyen CD, Ullah MA, Sebina I, et al. Synergism and antagonism of bacterial-viral coinfection in the upper respiratory tract. mSphere. 2022;7(1):e0098421.
30. Nickbakhsh S, Mair C, Matthews L, Reeve R, Johnson PCD, Thorburn F, et al. Virus-virus interactions impact the population dynamics of influenza and the common cold. Proc Natl Acad Sci U S A. 2019;116(52):27142–50.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Comparison of the Effects of Femoral Nerve Block and Adductor Canal Block on Postoperative Analgesia in Patients to Undergo Unilateral Knee Arthroplasty

Tek Taraflı Diz Artroplastisi Geçirecek Hastalarda Femoral Sinir Bloğu ile Adduktor Kanal Bloğunun Postoperatif Analjezi Üzerine Etkilerinin Karşılaştırılması

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ABSTRACT

Aim: *Total knee arthroplasty (TKA) is a major orthopedic procedure often associated with significant postoperative pain. Effective pain management is critical for early mobilization, rehabilitation, and reducing complications such as chronic pain. With the increasing use of ultrasound in regional anesthesia, the frequency of femoral nerve block (FNB) and adductor canal block (ACB) for analgesia after TKA is rising. This study aimed to compare the effects of femoral nerve block and adductor canal block on postoperative analgesia in patients undergoing unilateral knee arthroplasty.*

Material and Methods: *The study was conducted with the approval of the ethics committee, and written consent was obtained from the patients. It was carried out on 70 patients aged 18–70, with an American Society of Anesthesiologists (ASA) score of I-II, who planned to undergo elective TKA surgery. The study was designed as a prospective, randomized, and single-blind trial. Demographic data of the patients were recorded, and routine monitoring and general anesthesia induction were performed. Patients were divided into two groups: those who received FNB (Group F) and those who received ACB (Group A). Both groups were administered 20 mL of 0.375% bupivacaine. Heart rate (HR) and mean arterial pressure (MAP) were recorded intraoperatively before and after induction and every 30 minutes. In the postoperative period, patient-controlled analgesia (PCA) with intravenous tramadol was applied. Total tramadol usage and the number of times analgesia was needed were recorded. HR, MAP, and visual analog scale (VAS) scores were recorded at postoperative 30 minutes, 1, 2, 4, 6, 12, and 24 hours. Complications (nausea/vomiting, hypotension, bradycardia, itching) were recorded for 24 hours.*

Results: *Mean VAS scores were significantly lower in the FNB group at postoperative 0, 1, 2, and 6 hours ($p<0.05$). Total tramadol consumption and bolus requests were higher in the ACB group ($p<0.001$). Both techniques achieved VAS scores below 4, with no significant differences in additional analgesic use or complications. Nausea and vomiting rates were 5% (FNB) and 10% (ACB). No significant differences were observed in perioperative and postoperative MAP or HR between the groups.*

Conclusions: *Femoral nerve block and ACB provide effective analgesia after TKA, with VAS scores below 3 and high patient satisfaction. However, FNB demonstrated superior early postoperative pain control and lower opioid consumption. ACB, as a sensory block, is advantageous for minimizing quadriceps weakness and should be considered part of multimodal analgesia strategies. It was concluded that femoral nerve block is more effective in providing postoperative analgesia for patients undergoing unilateral knee arthroplasty.*

Keywords: *total knee arthroplasty; femoral nerve block; adductor canal block; multimodal analgesia; postoperative analgesia*

ÖZET

Amaç: *Total diz artroplastisi (TDA) sonrası ağrı şiddetlidir ve tedavi edilmediğinde kronikleşebilir. Ultrasonografinin rejyonel anestezide kullanımında artmasıyla beraber TDA sonrası analjezi amacıyla femoral sinir bloğu (FSB) ve adduktor kanal bloğu (AKB) uygulama sıklığı artmaktadır. Çalışmamızda tek taraflı diz artroplastisi geçirecek hastalarda femoral sinir bloğu ve adduktor kanal bloğunun postoperatif analjezi üzerine etkilerinin karşılaştırılmayı amaçladık.*

Gereç ve Yöntem: *Çalışma, etik kurulu onayı, hastalardan yazılı izin alınarak, elektif TDA cerrahisi uygulanacak American Society of Anesthesiologists (ASA) skoru I-II olan 18–70 yaş grubu 70 hastada gerçekleştirildi. Çalışma prospektif, randomize ve tek kör olarak planlandı. Hastaların demografik verileri kaydedilerek rutin monitörizasyon ve genel anestezi indüksiyonu uygulandı. Hastalar FSB (Grup F) ve AKB (Grup A) yapılan grup olarak ikiye ayrıldı. Her iki gruba 20 mL %0,375 bupivakain uygulandı. Tüm hastaların kalp atım hızı (KAH) ve ortalama arter basıncı (OAB) indüksiyon öncesi, indüksiyon sonrası ve intraoperatif her 30 dakikada bir kaydedildi. Postoperatif dönemde intravenöz tramadol ile hasta kontrollü analjezi (HKA) uygulandı. Toplam kullanılan tramadol miktarı ve kaç defa analjezi ihtiyacı olduğu kaydedildi. KAH, OAB ve vizüel analog skala (VAS) skoru postoperatif 30 dk, 1, 2, 4, 6, 12 ve 24. saatlerde kaydedildi. Komplikasyonlar 24 saat boyunca (bulantı/kusma, hipotansiyon, bradikardi, kaşıntı) kaydedildi.*

Bulgular: *Demografik verilerde, intraoperatif ve postoperatif hemodinamik verilerde, ek analjezik ihtiyacı ve komplikasyonlar her iki grupta istatistiksel olarak anlamlı fark bulunmadı ($p>0,05$). Postoperatif VAS skorları, kullanılan toplam tramadol miktarı istatiksel olarak Grup F'de anlamlı düşük bulundu.*

Sonuç: *Tek tek taraflı diz artroplastisi geçirecek hastalarda femoral sinir bloğunun postoperatif analjezi üzerine daha etkin olduğunu sonucuna ulaşıldı.*

Anahtar kelimeler: *total diz artroplastisi; femoral sinir bloğu; adduktor kanal bloğu; multimodal analjezi; postoperatif analjezi*

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Introduction

Total knee arthroplasty (TKA) is an effective obstetric surgery method with good results for patients with advanced gonarthrosis whose demand for conservative treatment is increasing day by day with the aging population[1,2]. The postoperative period following this major orthopedic procedure is often associated with moderate to severe pain[3]. The primary goals after TKA should include minimizing the patient's pain, accelerating the recovery process, enhancing patient comfort, speeding up mobilization, avoiding or effectively preventing side effects, and reducing treatment costs[4]. To achieve these goals, multimodal analgesia methods, such as epidural catheter-assisted patient-controlled analgesia, intravenous patient-controlled analgesia, peripheral nerve blocks, and intraoperative intra-articular local anesthetic infiltration, can be utilized in postoperative pain management[5]. Traditional pain control methods, including intravenous and oral pain medications, have been associated with unreliable pain control and negative effects such as hypotension, sedation, urinary retention, and nausea[6]. Despite the advantages of epidural blocks in analgesia for knee arthroplasty, serious side effects associated with central blocks (motor block, urinary retention, hypotension, bradycardia, nausea, and/or vomiting, etc.) are acknowledged. Among these methods, peripheral nerve blocks are becoming increasingly popular due to their benefits during the perioperative period and relatively fewer side effects than other techniques.

The commonly used peripheral nerve blocks in TKA perioperative analgesia include femoral, obturator, sciatic, lumbar plexus, and adductor canal nerve blocks[7]. These blocks can be performed as single or combination blockages and administered as single injections or continuous infusions.

With the femoral nerve block (FNB), anesthesia is provided for the anterior and medial aspects of the thigh and knee and part of the medial aspect of the leg and ankle. It can be applied as a single injection or continuously through a catheter. While it can provide analgesic effects for 12–24 hours, this effect can extend to 48 hours[8]. The advantages of this block include reduced opioid usage, earlier mobilization, improved pain scores, and decreased hospital stay. However, the most significant disadvantage is that femoral nerve block may cause quadriceps muscle weakness and increase the risk of falls during the early postoperative period.

The adductor canal block (ACB) anesthetizes the anterior and medial parts of the knee, the area from the upper pole of the patella to the proximal tibia, the leg, the ankle, and part of the medial aspect of the foot. It can be administered as a single injection or continuously, similar to the femoral nerve block. The analgesic effect is similar to the femoral block for postoperative analgesia. Since it is a sensory block, it does not cause quadriceps weakness[9].

Applications of femoral nerve and adductor canal blocks are gradually becoming more widespread in TKA surgeries. This study prospectively compares the effectiveness, reliability, and postoperative pain control of femoral nerve block and adductor canal block. In this context, our study aims to contribute to the optimal selection of nerve blocks in analgesia management after TKA surgery, providing an important guide for clinical applications.

Material and Methods

This study was conducted in a tertiary-care medical center. Written and verbal informed consent was obtained from patients undergoing elective knee arthroplasty and classified into the ASA I-II group, aged 55 years and above. Ethical approval for the study was obtained from the Ethical Committee of Şişli Hamidiye Etfal Training and Research Hospital on May 14, 2019, with decision number 1247 under the Helsinki Declaration. The study was designed as randomized, prospective, and single-blind. Considering a large effect size (effect size=0.8), the alpha significance level was set at 0.05, and the sample size was calculated to be 70 individuals for 95% power. Patients who did not consent to participate in the study, those in ASA III-IV group emergencies, those with a local anesthetic allergy or allergic reactions after local anesthetic administration, those with infections in the area to be blocked, coagulation disorders, morbid obesity (BMI >40 kg/m^2), severe organ failure, neurological deficits in the past, psychiatric illnesses, and a chronic pain history were excluded from the study. Patients included in the study were informed about patient-controlled analgesia and visual analog scale (VAS) scoring during the preoperative evaluation.

Patients were divided into two groups using the closed envelope randomization method: the femoral nerve block group (Group F, n: 35) and the adductor canal block group (Group A, n: 35). All patients were taken to the regional block application room

for 30 minutes prior the operation for routine monitoring and premedication. The patients' names, ages, heights, weights, and timing of block placement were recorded. A femoral nerve block was performed under the fascia iliaca in Group F in the iliopsoas muscle sulcus. In contrast, in Group A, a saphenous nerve block was performed within the adductor canal. Both groups received 20 ml of 0.375% bupivacaine as a local anesthetic. The success of the block was evaluated in Group F by the absence of motor movements and through the pinprick test in the saphenous nerve area. Group A also assessed this using the pinprick test in the saphenous nerve area. Patients who reported paresthesia after the block were taken to the operating room. Routine monitoring consisting of fingertip saturation, heart rate (HR), and noninvasive mean arterial pressure (MAP) were monitored and recorded. General anesthesia was administered to all patients. Heart rate and noninvasive blood pressure were recorded before induction, after induction, at surgical incision, and every 30 minutes throughout the operation.

For postoperative analgesia, each patient was provided with intravenous patient-controlled analgesia containing tramadol. The total tramadol used and the number of requested versus administered boluses were recorded. Visual analog scale scores, HR, and MAP were recorded at 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, and 24 hours after the surgery. Complications such as hypotension, bradycardia, and itching were recorded for 24 hours.

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) program version 15.0 for Windows. Descriptive statistics were presented as numbers and percentages for categorical variables and mean and standard deviation for numerical variables. Comparisons between two independent groups were made using the Student's t-test when numerical variables met the normal distribution conditions and the Mann-Whitney U test when they did not. The Chi-Square Test was used to compare proportions among independent groups. Changes among independent groups during follow-up were analyzed using Repeated Measures ANOVA for changes and level differences. Comparisons of two dependent groups among the groups were conducted using a Paired t-test if the differences met the normal distribution condition or Wilcoxon Analysis if they did not. A significance level of α=0.05 was used, with p-values less than 0.05 considered statistically significant.

Results

A total of 70 patients were included in the study. When comparing the characteristics and surgical times of the patients, no statistically significant differences were found between the groups (Table 1). In perioperative mean arterial pressure (Figure 1) and heart rate (Figure 2), there was no statistically significant difference in follow-up means between both groups ($p>0.05$). In within-group analysis, statistically significantly higher arterial pressure and heart rate levels were found when comparing the baseline values with all measured time points ($p<0.001$). For postoperative mean arterial pressure (Figure 3) and heart rate (Figure 4), no statistically significant difference was observed in follow-up means between the two groups ($p>0.05$). In within-group evaluations, statistically significantly higher mean arterial pressure and heart rate levels were observed when comparing the baseline values with all measured hours ($p<0.001$).

Table 1. *Characteristics of patients and duration of operation*

	Adductor canal block		Femoral block		
	Mean±SD	Median	Mean±SD	Median	p
Age	63.1±4.7	63	63.9±3.8	64	0.421
Weight	84.4±8.4	85	85.7±5.6	86	0.442
Height	162.8±8.2	161	162.7±5.6	162	0.946
BMI	31.9±3.3	32.0	32.4±2.7	33.1	0.472
Time	126.7±9.6	125	131.7±17.2	125	0.440

Data were expressed as Mean±SD. P<0.05 was considered significant.

Table 2. *VAS score averages*

		Adductor canal block		Femoral block		
		Mean±SD	Median	Mean±SD	Median	p
VAS	Postoperative 0.min	2.97±0.62	3	2.63±0.55	3	0.021*
	Postoperative 1.hr	2.66±0.48	3	2.23±0.49	2	0.001*
	Postoperative 2.hr	2.46±0.51	2	2.17±0.51	2	0.027*
	Postoperative 4.hr	2.23±0.43	2	2.06±0.34	2	0.070
	Postoperative 6.hr	2.26±0.44	2	1.97±0.51	2	0.019*
	Postoperative 12.hr	2.06±0.34	2	1.86±0.55	2	0.666
	Postoperative 24.hr	1.71±0.57	2	1.54±0.51	2	0.227

Data are expressed as Mean±SD. *Statistically high. P<0.05.

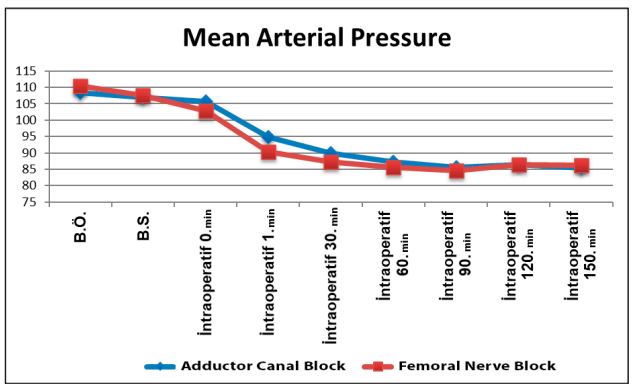

Figure 1. *Perioperative mean arterial pressure.*

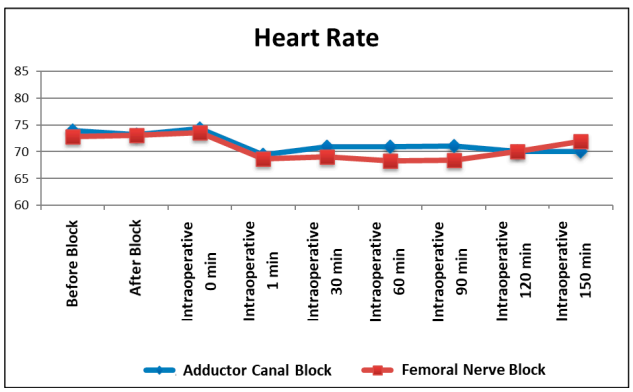

Figure 2. *Perioperative heart rate.*

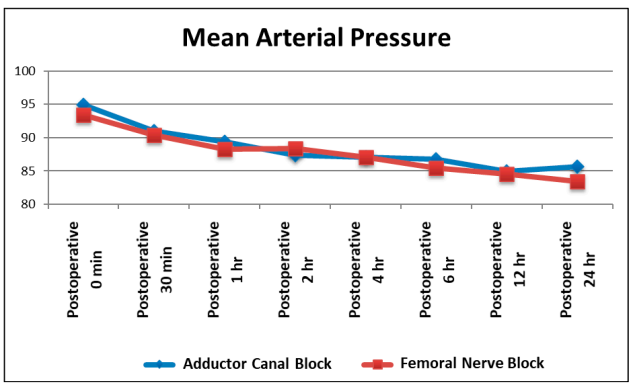

Figure 3. *Postoperative mean arterial pressure.*

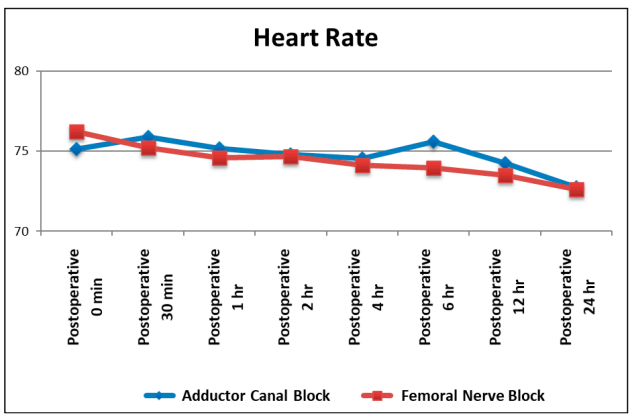

Figure 4. *Postoperative heart rate.*

Mean VAS values for the adductor canal block group were statistically significantly higher than those of the femoral block group at postoperative 0., 1., 2., and 6. hours (p>0.05) (Table 2). In within-group evaluations, VAS values at 2., 4., 6., 12., and 24. hours were statistically significantly lower compared to the VAS values at postoperative 0. hour in the adductor canal block (p<0.001). In the femoral block group, the VAS values were statistically significantly lower in all time intervals when compared to the VAS values at postoperative 0. hour (p<0.001). In terms of patient-controlled analgesia use, the requested boluses, administered boluses, and total tramadol doses were all found to be higher in the adductor canal block group compared to the femoral block group (p<0.001) (Table 3). No statistically significant differences were found regarding the use of additional analgesics between the groups. No statistically significant differences were observed in the complication rates between the groups (p>0.05) (Table 4).

Table 3. *Use of patient controlled analgesia*

	Adductor canal block		Femoral block		
	Mean±SD	Median	Mean±SD	Median	p
Requested bolus	15.3±2.1	15	11.7±2.2	11	<0.001*
Delivered bolus	12.4±1.3	12	9.3±1.8	9	<0.001*
Total tramadol	248.6±25.3	240	185.7±35.2	180	<0.001*

Data are expressed as Mean±SD. *Statistically high. P<0.05.

Table 4. *Complication incidence rates*

	Adductor canal block		Femoral block		
	n	%	n	%	p
Nausea/vomiting	4	11.4	2	5.7	0673
Hypotension	0	0.0	0	0.0	-
Bradycardia	0	0.0	1	2.9	1.000
Toxicity	0	0.0	0	0.0	-

Data are expressed as a percentage. P<0.05 is significant.

Discussion

The postoperative period following total knee arthroplasty (TKA), one of the major orthopedic interventions, is very painful, and many methods and medications have been tried to eliminate this pain, resulting in numerous studies. Optimal pain management and proper physiotherapy promote joint mobility, accelerating functional recovery processes[4,10]. Today, multimodal analgesia is recognized as an effective method for pain management after TKA[4]. Multimodal analgesia is a technique that provides quality analgesia, reduces opioid-related side effects, and delivers sufficient analgesia through additive or synergistic effects among different analgesics[11]. Peripheral nerve blocks are utilized as part of preemptive and multimodal analgesia[12].

A limited number of studies have evaluated the effects of preoperative block application on perioperative and postoperative hemodynamics[13]. In the literature, blocks have mostly been performed during the postoperative period. Our study evaluated the effects of preemptive peripheral nerve blocks on hemodynamics by recording HR and MAP data before the block, after induction, and every 30 minutes. No significant differences were observed between the groups in the preoperative and postoperative periods.

Zhen et al. (2018) applied ACB and FNB to patients undergoing TKA[14]. They studied VAS scores over the postoperative 72 hours. While the VAS scores measured in the first 24 hours were significantly lower in the FNB group, they found that the scores were similar at 48 and 72 hours. Thacher et al. (2017) examined the risk of knee collapse/falls in patients undergoing TKA in a retrospective study comparing femoral nerve block with adductor canal block and found similar VAS scores[15]. Karkhur et al. performed a meta-analysis of 13 articles on postoperative analgesia with adductor canal and femoral nerve blocks in TKA and found similar VAS scores among patients[10]. Another meta-analysis conducted in 2017 compared 12 randomized controlled trials and found similar postoperative VAS scores[16]. Kim H et al., in a prospective randomized controlled study, found the pain scores, especially at the postoperative 6th and 8th hours, to be lower in the group receiving FNB but observed a similarity in the VAS scores at the 48th hour[17]. In our study, VAS scores were below 4 in both groups during the first 24 hours. Although the VAS values were lower in the femoral nerve block group during the first 6 hours compared to the adductor canal block group, only 1 patient in the FNB group and 3 in the ACB group received rescue analgesics. In our study, we primarily focused on VAS values and opioid consumption during the first 24 hours postoperatively, while other studies investigated VAS values for 48 or even 72 hours postoperatively.

In patients undergoing total knee arthroplasty receiving ACB, they were divided into two groups; one group received a single administration of 30 cc of 0.25% bupivacaine, while the other group received continuous infusion through a catheter; it was shown that in the continuous infusion group, pain scores, analgesic consumption, and the pain scores were lower[18]. Shah, Jain et al. demonstrated that the adductor canal can be filled with 30 cc of local anesthetic[19]. Lund et al. also showed that the adductor canal could be filled with 30 cc when imaged with MRI[20]. Our study used 20 cc of 0.375% bupivacaine under ultrasound guidance in both nerve blocks. While sufficient analgesia was provided with these local anesthetic volumes in both blocks, VAS values were lower in the femoral group during the first 6 hours, and analgesic consumption was lower during the first 24 hours.

In studies where general anesthesia and spinal anesthesia techniques were applied with FNB and ACB,

postoperative follow-ups showed that opioid consumption and VAS scores were higher in patients receiving general anesthesia for both block technique[21]. In our study, general anesthesia was preferred after the block application. Due to our hospital's physical conditions and insufficient technical equipment, only 24-hour monitoring was possible. In this case, the choice of general anesthesia was made to avoid repeating invasive interventions and because inadequate feedback would be obtained during the 24-hour monitoring period.

Studies comparing FNB and ACB have found that morphine is usually used as an analgesic in patient-controlled analgesia applications. They found the amount of morphine consumed to be similar in both groups[22]. Our study chose tramadol in patient-controlled analgesia due to the absence of respiratory depression, itching, and vesicular glob formation. The average tramadol consumption was 185 mg in the femoral group and 245 mg in the adductor group.

Other studies have shown that in patients who exclusively used opioids for analgesia following total knee arthroplasty, the incidence of nausea and vomiting has increased[23]. The incidence of nausea and vomiting has decreased due to the reduced postoperative opioid consumption with regional techniques. In studies comparing FNB and ACB, although there was a 10% incidence of nausea and vomiting in studies applying patient-controlled morphine postoperatively, the incidence of nausea and vomiting was found to be similar for both techniques[10,16,24]. In our study, nausea and vomiting were detected in 2 patients (5%) in the femoral group and 4 patients (10%) in the adductor canal block group, but no significant difference was observed. We attributed the reduced perioperative and postoperative opioid consumption to the use of regional techniques despite the severe pain experienced in TKA surgeries.

The 24-hour follow-up for patients may be viewed as a significant limitation of our study. A longer duration is necessary to evaluate potential postoperative complications. Since mobilization was not permitted within the first 24 hours by the orthopedic clinic, complications related to quadriceps weakness could not be evaluated. Additionally, due to the lack of permission for ambulation, only resting VAS scores could be assessed.

There has been no consensus in studies regarding the type of anesthetic agents, dosages, and timing. Due to the heterogeneity of studies and their results, there is no agreement on the optimal anesthetic agent, dosage, method of application, and duration[22,25–27].

In our study, finding VAS values below 3 and high patient satisfaction in operations like TKA, which are associated with high postoperative pain intensity, demonstrates that both can be used as effective postoperative analgesia methods.

Conclusion

In major orthopedic procedures such as TKA, where severe postoperative pain is observed and can transform into chronic pain if untreated, either type of block can be performed for effective analgesia. Given that early mobilization, ambulation, and physical therapy following TKA accelerate the functional recovery process, the adductor canal block, which is sensory only and does not cause quadriceps weakness, should be considered a part of multimodal analgesia. In our study, the total opioid consumption, VAS scores, and incidence of complications such as nausea and vomiting were lower in the group receiving preoperative femoral nerve block compared to the group receiving adductor canal block. For these reasons, we believe femoral nerve block to be more effective than adductor canal block for patients with planned TKA.

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First of all, I would like to express my sincere gratitude to Birsen Ekşioğlu Karaci for her support and guidance throughout the preparation of this thesis. The insights and feedback of Birsen Ekşioğlu Karaci have helped shape the scope and directions of this study. She passed away before this thesis was prepared as an article. May she rest in peace.

References

1. Li JW, Ma YS, Xiao LK. Postoperative pain management in total knee arthroplasty. Orthop Surg. 2019;11:755–761.
2. Karahan M, Acar E, Serarslan U, Gültekin A. Medial pivot total knee arthroplasty: Mid-term results. Acta Orthopaedica Belgica. 2023;89(1):97–102.
3. Seo SS, Kim OG, Seo JH, Kim DH, Kim YG, Park BY. Comparison of the effect of continuous femoral nerve block and adductor canal block after primary total knee arthroplasty. Clin Orthop Surg. 2017;9:303–309.
4. Dimaculangan D, Chen JF, Borzio RB, Jauregui JJ, Rasquinha VJ, Maheshwari AV. Periarticular injection and continuous femoral nerve block versus continuous femoral nerve block alone on postoperative opioid consumption and pain control following total knee arthroplasty: Randomized controlled trial. J Clin Orthop Trauma. 2019;10(1):81–86.
5. Horlocker TT, Kopp SL, Pagnano MW, Hebl JR. Analgesia for total hip and knee arthroplasty: a multimodal pathway featuring peripheral nerve block. J Am Acad Orthop Surg. 2006;14(3):126–135.
6. Toftdahl K, Nikolajsen L, Haraldsted V, Madsen F, Tønnesen EK, Søballe K. Comparison of peri- and intraarticular analgesia with femoral nerve block after total knee arthroplasty: A randomized clinical trial. Acta Orthop. 2007;78(2):172–179.
7. Hasegawa M, Singh D, Urits I, Pi M, Nakasone C, Viswanath O, Kaye AD. Review on Nerve Blocks Utilized for Perioperative Total Knee Arthroplasty Analgesia. Orthop Rev (Pavia). 2022;14(3):37405.
8. Szczukowski MJ Jr, Hines JA, Snell JA, Sisca TS. Femoral nerve block for total knee arthroplasty patients: a method to control postoperative pain. J Arthroplasty. 2004;19(6):720–5.
9. Berikashvili LB, Yadgarov MY, Kuzovlev AN, Smirnova AV, Kadantseva KK, Kuznetsov IV, Polyakov PA, Likhvantsev VV. Adductor Canal Block Versus Femoral Nerve Block in Total Knee Arthroplasty: Network Meta-Analysis. Clin J Pain. 2024;40(7):447–457.
10. Karkhur Y, Mahajan R, Kakralia A, Pandey AP, Kapoor MC. A comparative analysis of femoral nerve block with adductor canal block following total knee arthroplasty: A systematic literature review. J Anaesthesiol Clin Pharmacol. 2018;34(4):433–438.
11. Parvataneni HK, Shah VP, Howard H, Cole N, Ranawat AS, Ranawat CS. Controlling pain after total hip and knee arthroplasty using a multimodal protocol with local periarticular injections: a prospective randomized study. J Arthroplasty. 2007;22(6 Suppl 2):33–8.
12. Starks I, Wainwright T, Middleton R. Local anaesthetic infiltration in joint replacement surgery: What is its role in enhanced recovery?. International Scholarly Research Notices. 2011;2011(1):742927.
13. Chelly JE, Greger J, Gebhard R, Coupe K, Clyburn TA, Buckle R, Criswell A. Continuous femoral blocks improve recovery and outcome of patients undergoing total knee arthroplasty. The Journal of Arthroplasty. 2001;16(4):436–445.
14. Tan Z, Kang P, Pei F, Shen B, Zhou Z, Yang J. A comparison of adductor canal block and femoral nerve block after total-knee arthroplasty regarding analgesic effect, effectiveness of early rehabilitation, and lateral knee pain relief in the early stage. Medicine. 2018;97(48):e13391.
15. Thacher RR, Hickernell TR, Grosso MJ, Shah R, Cooper HJ, Maniker R, et al. Decreased risk of knee buckling with adductor canal block versus femoral nerve block in total knee arthroplasty: a retrospective cohort study. Arthroplasty Today. 2017;3(4):281–285.
16. Wang D, Yang Y, Li Q, Tang SL, Zeng WN, Xu J, et al. Adductor canal block versus femoral nerve block for total knee arthroplasty: a meta-analysis of randomized controlled trials. Scientific Reports. 2017;7(1):40721.
17. Kim DH, Lin Y, Goytizolo EA, Kahn RL, Maalouf DB, Manohar A, et al. Adductor canal block versus femoral nerve block for total knee arthroplasty: a prospective, randomized, controlled trial. Survey of Anesthesiology. 2014;58(4):199–200.
18. Canbek U, Akgun U, Aydogan NH, Kilinc CY, et al. Continuous adductor canal block following total knee arthroplasty provides a better analgesia compared to single shot: a prospective randomized controlled trial. Acta Orthopaedica et Traumatologica Turcica. 2019;53(5):334–339.
19. Shah NA, Jain NP. Is continuous adductor canal block better than continuous femoral nerve block after total knee arthroplasty? Effect on ambulation ability, early functional recovery and pain control: a randomized controlled trial. The Journal of Arthroplasty. 2014;29(11):2224–2229.
20. Lund J, Jenstrup MT, Jaeger P, Sørensen AM, Dahl JB. Continuous adductor-canal-blockade for adjuvant post-operative analgesia after major knee surgery: preliminary results. Acta Anaesthesiologica Scandinavica. 2011;55(1):14–19.
21. Gonano C, Leitgeb U, Sitzwohl C, Ihra G, Weinstabl C, Kettner SC. Spinal versus general anesthesia for orthopedic surgery: anesthesia drug and supply costs. Anesthesia & Analgesia. 2006;102(2):524–529.
22. Patterson ME, Bland KS, Thomas LC, Elliott CE, Soberon Jr JR, Nossaman BD, Osteen K. The adductor canal block provides effective analgesia similar to a femoral nerve block in patients undergoing total knee arthroplasty -a retrospective study. Journal of Clinical Anesthesia. 2015;27(1):39–44.
23. Ryu JH, Jeon YT, Min B, Hwang JY, Sohn HM. Effects of palonosetron for prophylaxis of postoperative nausea and vomiting in high-risk patients undergoing total knee arthroplasty: A prospective, randomized, double-blind, placebo-controlled study. PLoS One. 2018;13(5):e0196388.
24. Ludwigson JL, Tillmans SD, Galgon RE, Chambers TA, Heiner JP, Schroeder KM. A comparison of single-shot adductor canal block vs femoral nerve catheter for total knee arthroplasty. The Journal of Arthroplasty. 2016;31(3):741.
25. Elkassabany NM, Antosh S, Ahmed M, Nelson C, Israelite C, Badiola I., et al. The risk of falls after total knee arthroplasty with the use of a femoral nerve block versus an adductor canal block: a double-blinded randomized controlled study. Anesthesia & Analgesia. 2016;122(5):1696–1703.
26. Grevstad U, Mathiesen O, Valentiner LS, Jaeger P, Hilsted KL, Dahl JB. Effect of adductor canal block versus femoral nerve block on quadriceps strength, mobilization, and pain after total knee arthroplasty: a randomized, blinded study. Regional Anesthesia & Pain Medicine. 2015;40(1):3–10.
27. Machi AT, Sztain JF, Kormylo NJ, Madison SJ, Abramson WB, Monahan AM, et al. Discharge readiness after tricompartment knee arthroplasty: adductor canal versus femoral continuous nerve blocks—a dual-center, randomized trial. Anesthesiology. 2015;123(2):444–456.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Cardiac Autonomous Functions in Patients with Chronic Glomerulonephritis

Kronik Glomerülonefrit Hastalarında Kardiyak Otonom Fonksiyonların Değerlendirilmesi

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ABSTRACT

Aim: *Our study aims to investigate the presence of autonomic dysfunction, which is one of the important causes of cardiovascular mortality, by evaluating heart rate variability and heart rate turbulence in patients with chronic glomerulonephritis*

Material and Methods: *In this case-control study, 42 individuals with chronic glomerulonephritis classified as stage 1–3 chronic kidney disease and 102 age- and sex-matched healthy subjects were compared in terms of heart rate variability and heart rate turbulence. Subgroup analyses were performed by dividing the patient group into nephrotic and nephritic syndrome subgroups. p<0.05 was accepted as significant.*

Results: *In the glomerulonephritis group, significant decreases were observed in heart rate variability parameters, indicating that cardiac autonomic functions changed in favor of sympathetic activation. When subgroup analysis was performed, it was observed that the decrease in the parameters representing parasympathetic activation of heart rate variability continued in the nephritic syndrome group.*

Conclusions: *This study demonstrated that autonomic dysfunction characterized by parasympathetic suppression and sympathetic activation is present in patients with chronic glomerulonephritis, even in the early stages of chronic kidney disease.*

Key words: *glomerulonephritis, cardiac autonomic function, heart rate variability, heart rate turbulence*

ÖZET

Amaç: *Çalışmamızın amacı, kronik glomerülonefrit hastalarında, kalp hızı değişkenliği (KHD) ve kalp hızı türbülansı (KHT) değerlendirmesiyle, kardiyovasküler mortalitenin önemli nedenlerinden birisi olan otonom disfonksiyon varlığının araştırılmasıdır.*

Gereç ve Yöntem: *Bu vaka-kontrol çalışmasında evre 1–3 kronik böbrek hastalığı (KBH) olarak sınıflandırılan 42 kronik glomerülonefritli birey ile yaş ve cinsiyet açısından eşleştirilmiş 102 sağlıklı birey KHT ve KHD açısından karşılaştırıldı. Hasta grubu nefrotik ve nefritik sendrom alt gruplarına ayrılarak alt grup analizleri yapıldı. p<0,05 anlamlı kabul edildi.*

Bulgular: *Glomerülonefrit grubunda, KHD'nin önemli parametreleri olan SDNN, SDNN endeks, rMSSD, pNN50 ve HF değerlerinde kontrol grubuyla karşılaştırıldığında anlamlı düşüş gözlendi (p=0,046, p=0,031, p=0,019, p=0,013, p=0,032, sırasıyla). Subgrup analizi yapıldığında nefritik sendrom grubunda rMSSD ve pNN50 değerlerinde istatistiksel olarak anlamlı azalmanın devam ettiği görüldü. (sırasıyla p=0,049, p=0,032)*

Sonuç: *Bu çalışma ile kronik glomerülonefritli hastalarda KBH'nin erken evrelerinde dahi parasempatik baskılanma ve sempatik aktivite ile karakterize otonomik disfonksiyonun var olduğu gösterilmiştir.*

Anahtar kelimeler: *glomerülonefrit; kardiyak otonom fonksiyon; kalp hızı değişkenliği; kalp hızı türbülansı*

Introduction

Glomerulonephritis is a group of diseases characterized by immune damage and cell proliferation in the glomerular capillaries. Although it typically follows a chronic course, it can occasionally present with acute clinical manifestations such as rapidly progressive glomerulonephritis or acute nephritic syndrome. Glomerulonephritis is classified into nephritic and nephrotic syndromes based on its pathogenesis, histopathological appearance and clinical presentation[1]. Nephritic syndrome is characterized by the presence of antigen-antibody deposits on an inflammatory basis, and its clinical manifestations include hematuria, hypertension and edema. In nephrotic syndrome, proteinuria, hypoalbuminemia, hyperlipidemia and edema occur due to non-inflammatory immune-mediated

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damage where immune cells do not infiltrate the glomeruli[2,3]. Patients with chronic glomerulonephritis (CGN) –often accompanied by risk factors such as hypertension, hyperlipidemia and renal dysfunction– are considered to be at high risk for cardiovascular (CV) events[4].

Since the 1970 s, many studies have shown that impaired cardiac autonomic function in various diseases is associated with CV mortality[5–8]. In this context, studies investigating CV mortality in renal diseases have demonstrated that individuals with advanced chronic kidney disease (CKD) –including those with glomerulonephritis as the underlying etiology– exhibit impaired cardiac autonomic function[9]. However, this pathology remains unclear due to the limited number of studies focusing on patients with glomerulonephritis in the early stages of CKD.

With current technology, the most objective tests for assessing cardiac autonomic functions are heart rate variability (HRV) and heart rate turbulence (HRT). It has been shown that a reduction in these parameters plays a role in sudden cardiac death (SCD) and CV mortality[6–8], whereas an increase is beneficial for predicting atrial fibrillation[10]. Heart rate variability measures the variability in R-R intervals, which persist under controlled conditions. Time-domain indices of HRV include the standard deviation of normal to normal (NN) intervals (SDNN), standard deviations of all normal sinus NN intervals in 5-minute segments (SDNN index), the root mean square of differences between successive NN intervals (rMSSD) and percentage of adjacent NN intervals differing by more than 50 ms divided by the total number of NN intervals (pNN50). These measures are particularly useful for evaluating parasympathetic activity[11]. In contrast, frequency-domain analysis examines different spectral components: the high-frequency (HF) band reflects parasympathetic influences, while the low-frequency (LF) band includes both sympathetic and parasympathetic effects, with LF primarily serving as an indicator of sympathetic activity. The LF/HF ratio is commonly used to evaluate the balance between these two autonomic components[12]. Heart rate turbulence analyzes the autonomic modulatory response of the sinus node to a ventricular extrasystole (VES). It is assumed to consist of a combination of two neural reflexes: a baroreceptor-related increase in heart rate after a hemodynamically inefficient ventricular contraction (called TO; turbulence onset, which corresponds to the first RR interval shortening) and a reflex bradycardia resulting from increased ventricular filling which elevates arterial pressure after a compensatory pause (called TS; turbulence slope, which reflects the subsequent prolongation period)[13]. Heart rate variability and HRT are known to be the most important predictors of cardiac mortality in patients with acute myocardial infarction[7].

In this study, we aimed to investigate the presence of autonomic dysfunction, which is one of the important causes of CV mortality, in patients with CGN, which is classified within the early stages of CKD, using HRV and HRT parameters from 24-hour electrocardiographic (ECG) Holter monitoring.

Material and Methods

The study was conducted among patients who presented to the university hospital's cardiology and nephrology outpatient clinics between December 2019 and July 2022. Before the study, ethical approval was obtained from the local ethics committee (dated 28.09.2020, decision number 15/32, TÜTF-BAEK 2020/341 protocol document). The patient group (42 subjects) was selected from individuals with CGN who were followed in the nephrology outpatient clinic and had a definitive diagnosis confirmed by renal biopsy (8 patients with immunoglobulin A nephropathy, 2 with lupus nephritis, 6 with vasculitic nephropathy, 9 with membranous nephropathy, 14 with focal segmental glomerulosclerosis, and 3 with minimal change disease). Within the patient group, 16 patients were classified as having nephritic syndrome and 26 as having nephrotic syndrome, as determined in the subgroup analysis. The control group (102 subjects) was selected from individuals who attended the cardiology clinic, underwent 24-hour ECG Holter and transthoracic echocardiography (TTE) examinations, and were demographically matched to the patient group. Acute glomerulonephritis was excluded from the study due to its clinical course, which could affect hemodynamics and the autonomic nervous system (ANS). Since previous studies have shown cardiac autonomic dysfunction in coronary artery disease, diabetes mellitus, and stage 4–5 CKD, individuals with these conditions were excluded from the study. Additionally, individuals with pacemakers, those taking antiarrhythmic drugs or medications that affect ANS, and those with structural heart disease due to an increased risk of arrhythmia were also excluded.

Written informed consent was obtained from all patients. All TTE evaluations were performed using a 2.5–3.5 MHz transducer on the 'Vivid s70N, General Electric Health Care, Horten/Norway' echocardiography device. Data on age, gender, chronic diseases, and medications used were collected. Hypertension was defined as either a history of hypertension with a blood pressure of 140/90 or higher or the use of antihypertensive medication. Hyperlipidemia was defined as either receiving lipid-lowering treatment or meeting the criteria for such treatment according to the guidelines. Chronic glomerulonephritis patients were divided into nephrotic and nephritic syndrome groups for subgroup analysis based on the clinical presentation matching their histopathological findings. Based on histopathological findings, patients with proteinuria >3.5 g/day/1.73 m^2, hypoalbuminemia, and edema were classified as having nephrotic syndrome; those with hematuria, non-nephrotic proteinuria (<3.5 g/day/1.73 m^2), hypertension, edema and renal dysfunction were classified as having the nephritic syndrome. Patients who did not strictly meet the aforementioned hypertension criteria but exhibited elevated blood pressure and other clinical features more consistent with nephritic syndrome were included in the nephritic syndrome subgroup.

Electrocardiographic Holter evaluation: 24-hour Holter monitoring of all patients was performed with a 3-channel ECG recorder (DMS Holter Recorder, Biomedical Instruments Co. LTD., Beijing/China). These recordings obtained 24-hour average heart rate, RR variability and sinusoidal response to VES data. The recordings were visually inspected, and noisy regions were excluded from the analysis. The computer analyzed HRV and HRT parameters (Biomedical Instruments Co. LTD., Holter Software, China software). The power spectrum analysis of the frequency parameters of HRV was performed by the "Fast Fourier" transform. According to power spectrum analysis, 0.16–0.40 was considered high frequency (HF; high frequency), 0.04–0.15 as low frequency (LF; low frequency). Normalized (nu) values of low-frequency and high-frequency parameters calculated according to the formula below were used: LF (nu)=LF (100/ Total Power), HF (nu)=HF (100/ Total Power). Heart rate variability parameters were evaluated according to the North American Battery and Electrophysiological Society guidelines and the European Society of Cardiology[14].

When HRT analysis was first introduced, taking at least 5 appropriate VESs for accurate calculation in HRT evaluation was recommended since the reliability of measurements would decrease in patients with few VESs due to factors such as sinus arrhythmia and parasites[15]. However, later studies reported that a single appropriate VES may be sufficient for baroreflex assessment[16]. In this study, to perform more HRT evaluation in patients, all records were scanned and beats with arrhythmia, interference or misclassification in 5 sinus beats before VES and 15 sinus beats after compensatory pause were excluded from the analysis. Thus, HRT measurements were performed in patients with one or more VESs. Schmidt criteria were used in the calculation of TO and TS[7]. Calculation of turbulence initial value; $T0=[(RR_1+RR_2)-(RR_{-2}+RR_{-1})] / (RR_{-2}+RR_{-1}) \times 100$. This study considered TO ≥%0 and TS ≥2.5 ms/RR value pathological.

Statistical analysis: The normality condition for continuous variables was checked using the Shapiro-Wilk test. Normally distributed data were compared between two groups with Student's t-test and between three or more groups with One-way analysis of variance (Post-Hoc: Tukey HSD and Fisher's LSD test). When the data were not normally distributed, the Mann-Whitney U test and Kruskal Wallis H test (Post-Hoc: Dunn test) were used instead of these tests. Pearson's Chi-square test and Fisher's Exact test examined the relationship between two categorical variables. The Kaplan-Meier method examined Glomerulonephritis durations according to microalbuminuria groups in 24-hour urine (<30 mg/day, 30–300 mg/day and >300 mg/day). The Mantel-Cox Log Rank test was used to investigate whether there was any significance between the groups. The Kaplan Meier method used the RStudio (survival v. 3.4 and survminer v. 0.4.9 packages) program. IBM Statistical Package for Social Sciences (SPSS) program version 23 (IBM Inc., Armonk, NY) was used for all other analyses. The significance level was determined as $p < 0.05$.

Results

A total of 144 patients participated in the study. Of these, 42 were in the patient group (16 with nephritic syndrome and 26 with nephrotic syndrome), and 102 were in the control group. The patient and healthy groups were similar concerning demographic characteristics and echocardiographic findings. When laboratory values were compared to those of healthy subjects,

patients with glomerulonephritis showed lower *modification of diet in renal disease glomerular filtration rate* (MDRD-GFR), total protein and albumin levels, as well as higher urea, creatinine, uric acid, potassium, phosphorus (all p<0.05) (Table 1). C-reactive protein (CRP) was lower in the patient group. However, this may not reflect the true situation due to variations in CRP kits and reference ranges during the study period.

In the 24-hour ECG Holter evaluation, all HRV values were lower in the patient group compared to the healthy group, and the LF/HF ratio was higher in the patient group, correlating with these results. Low SDNN, SDNN-index, rMSSD, pNN50 and HF values showed statistical significance (p=0.046, p=0.031, p=0.019, p=0.013, p=0.032, respectively). No significant differences regarding HRT parameters were found between the patient and healthy groups (Table 2).

During subgroup analysis, when the patients were divided into nephrotic and nephritic syndrome groups and compared with healthy subjects, no significant differences were observed in demographic and echocardiographic values. MDRD-GFR remained significantly lower in the nephritic syndrome group than in the healthy group subjects, whereas the decrease in the nephrotic syndrome group did not reach statistical significance. Total protein and albumin were significantly lower in both nephritic and nephrotic syndrome groups than in healthy subjects (Table 3).

Table 1. *Demographic characteristics, echocardiographic findings and laboratory values of the patient and healthy group*

	Patient group (n=42)	Healthy group (n=102)	p
Age, year	48.45±12.30	47.76±11.99	0.757*
Gender			
Female	13 (30.95)	35 (34.31)	0.697
Male	29 (69.05)	67 (65.69)	
Hypertension			
No	22 (52.38)	69 (67.65)	0.084
Yes	20 (47.62)	33 (32.35)	
Hyperlipidemia			
No	29 (69.05)	66 (64.71)	0.617
Yes	13 (30.95)	36 (35.29)	
Echocardiography			
LVEF, %	64.5 (61.75–67.25)	63 (60–66)	0.168
LVEDD	47.67±3.45	47.23±3.92	0.527*
LVESD	30 (27–31,25)	30 (26–33)	0.841
IVS	10 (9–11)	10 (9–11)	0.578
PWT	10 (9–11)	10 (9–11)	0.481
Laboratory			
MDRD-GFR	82.5 (50.25–110)	99 (89–108,25)	**0.006**
Urea, mg/dL	45 (29.75–67.25)	29 (24–34.25)	**<0.001**
Creatinine, mg/dL	1.05 (0.8–1.52)	0.8 (0.69–0.9)	**<0.001**
Uric acid, mg/dL	6.1 (5.18–7.05)	5 (3.9–5.6)	**<0.001**
Fasting blood sugar, mg/dL	95.5 (89.75–105.5)	98 (92–103)	0.671
Sodium, mmol/L	140 (138–142.25)	140 (139–141)	0.714
Potassium, mmol/L	4.57±0.43	4.41±0.33	**0.017***
Chlorine, mmol/L	104 (102–105.25)	104 (102–106)	0.945
Total calcium, mg/dL	9.5 (9.1–9.7)	9.5 (9.28–9.8)	0.161
Phosphorus, mg/dL	3.67±0.51	3.38±0.54	**0.004***
Magnesium, mg/dL	2 (1.9–2.2)	2 (1.9–2.1)	0.705
Total protein, g/dL	6.7 (6.28–7.13)	7.2 (6.9–7.5)	**<0.001**
Albumin, g/dL	4.15 (3.7–4.4)	4.4 (4.1–4.6)	**<0.001**
CRP, mg/L	0.38 (0.3–1.23)	3 (1.3–4.7)	**<0.001**
HCT, %	41.35 (37.65–45.65)	42.5 (39.18–44.93)	0.416
TSH, ulU/mL	1.6 (0.9–3.03)	1.66 (1.17–2.35)	0.718

CRP; C-reactive protein, HCT; hematocrit, IVS; interventricular septum, LVEDD; left ventricular end-diastolic diameter, LVEF; left ventricular ejection fraction, LVESD; left ventricular end-systolic diameter, MDRD-GFR; Modification of Diet in Renal Disease-Glomerular Filtration Rate, PWT; posterior wall thickness, TSH; thyroid-stimulating hormone.

Table 2. *24-Hour ECG Holter results of the patient and healthy group*

	Patient group (n=42)	Healthy group (n=102)	p
SDNN, msn	125 (105.25–149.25)	140.5 (110.75–172)	**0.046**
SDNN-index	51.5 (41.75–60.75)	58 (48–69.5)	**0.031**
rMSSD, msn	23 (18.5–34)	29 (23–38)	**0.019**
pNN50, %	3.5 (1.75–10)	7 (4–13)	**0.013**
HF	118 (62.13–290)	208.5 (115.5–346.75)	**0.032**
LF	447.5 (263.5–637.75)	522.5 (333.75–747.75)	0.067
LF/HF	2.91 (1.7–4.55)	2.32 (1.55–4.15)	0.414
VLF	881.88±319.35	1008.76±415.95	0.079*
TO‡	-2.5 (-1.63-{-3.57})	-2.95 (-1.56-{-4.88})	0.546
TS‡	14.8 (8.59–26.7)	13.67 (8.59–22.19)	0.641

HF; high frequency, LF; low frequency, pNN50; percentage of differences between adjacent NN intervals >50 ms, rMSSD; root mean square of the successive differences, SDANN; standard deviation of 5 min averaged NN intervals, SDNN; standard deviation of all NN intervals, TO; turbulence onset, TS; turbulence slope, VLF; very low frequency. Data are shown as median (25th to 75th percentile) or mean ± standard deviation. Mann-Whitney U test, *: Student t test. ‡: Patient group: n=19, Healthy group: TO n=41, TS n=43.

Table 3. *Demographic characteristics, echocardiographic findings and laboratory values of nephritic syndrome, nephrotic syndrome and healthy group*

	Nephritic syndrome group (n=16)	Nephrotic syndrome group (n=26)	Healthy group (n=102)	p
Age, year	46.25±12.64	49.81±12.14	47.76±11.99	0.622*
Gender				
Female	6 (37.5)	7 (26.92)	35 (34.31)	0.723
Male	10 (62.5)	19 (73.08)	67 (65.69)	
Hypertension				
No	9 (56.25)	13 (50)	69 (67.65)	0.207
Yes	7 (43.75)	13 (50)	33 (32.35)	
Hyperlipidemia				
No	13 (81.25)	16 (61.54)	66 (64.71)	0.375
Yes	3 (18.75)	10 (38.46)	36 (35.29)	
Echocardiography				
LVEF	64.5 (62–66)	64.5 (60.75–68)	63 (60–66)	0.385
LVESD	48.06±3.94	47.42±3.16	47.23±3.92	0.712*
LVEDD	30 (27.25–32.75)	29.5 (27–30.25)	30 (26–33)	0.813
IVS	10 (9–11)	10 (9–11.25)	10 (9–11)	0.738
PWT	10 (9–11)	10 (9–11)	10 (9–11)	0.776
Laboratory				
MDRD-GFR	67 (50–107.25)[b]	89.5 (65.6–113.5)[a,b]	99 (89–108.25)[a]	**0.009**
Urea, mg/dL	62.5 (33.5–76.75)[a]	37.5 (27–57)[a]	29 (24–34.25)[b]	**<0.001**
Creatinine, mg/dL	1.38 (0.83–2.02)[a]	0.91 (0.79–1.33)[a]	0.8 (0.69–0.9)[b]	**<0.001**
Uric acid, mg/dL	6 (5.13–7.25)[a]	6.2 (5.13–7.05)[a]	5 (3.9–5.6)[b]	**<0.001**
Fasting blood sugar, mg/dL	95 (87.25–99.75)	98 (91.5–109)	98 (92–103)	0.365
Sodium, mmol/L	140 (138–141.75)	140 (138–143)	140 (139–141)	0.896
Potassium, mmol/L	4.56±0.42	4.57±0.45	4.41±0.33	0.057*
Chlorine, mmol/L	103.5 (102.2–105.7)	104 (102–105.25)	104 (102–106)	0.991
Total calcium, mg/dL	9.45 (8.95–9.8)	9.5 (9.1–9.63)	9.5 (9.28–9.8)	0.374
Phosphorus, mg/dL	3.77±0.51[a]	3.62±0.52[a,b]	3.38±0.54[b]	**0.010***
Magnesium, mg/dL	2.1 (2–2.2)[a]	2 (1.8–2.03)[b]	2 (1.9–2.1)[a,b]	**0.022**
Total protein, g/dL	6.55 (6.2–7.28)[b]	6.75 (6.3–7.1)[b]	7.2 (6.9–7.5)[a]	**<0.001**
Albumin, g/dL	4 (3.8–4.48)[b]	4.2 (3.68–4.33)[b]	4.4 (4.1–4.6)[a]	**<0.001**
CRP, mg/L	0.35 (0.2–1.48)[b]	0.38 (0.3–1.25)[b]	3 (1.3–4.7)[a]	**<0.001**
HCT, %	40.5 (34.38–43.88)	42 (38.75–47)	42.5(39.18–44.93)	0.317
TSH, ulU/mL	1.45 (0.66–2.53)	1.95 (1.15–3.6)	1.66 (1.17–2.35)	0.246

CRP; C-reactive protein, HCT; hematocrit, IVS; interventricular septum, LVEDD; left ventricular end-diastolic diameter, LVEF; left ventricular ejection fraction, LVESD; left ventricular end-systolic diameter, MDRD-GFR; Modification of Diet in Renal Disease-Glomerular Filtration Rate, PWT; posterior wall thickness, TSH; thyroid-stimulating hormone.

Table 4. *24-hour ECG holter results in nephritic syndrome, nephrotic syndrome and healthy groups*

	Nephritic syndrome group (n=16)	Nephrotic syndrome group (n=26)	Healthy group (n=102)	p
SDNN, msn	127.5 (99.25–141.5)	124 (107.5–155.25)	140.5 (110.75–172)	0.133
SDNN-indeks	50.5 (38.75–58.75)	52 (44.25–68.5)	58 (48–69.5)	0.067
rMSSD, msn	22 (16.75–30.25)[b]	24.5 (18.5–38.25)[a,b]	29 (23–38)[a]	**0.049**
pNN50, %	3 (1–7)[b]	4 (2–13.25)[a,b]	7 (4–13)[a]	**0.032**
HF	118 (58–264.73)	118 (64.38–345)	208.5 (115.5–346.75)	0.082
LF	341 (211.23–620.5)	490 (372–670.75)	522.5 (333.75–747.75)	0.059
LF/HF	2.68 (1.54–3.92)	3.09 (1.9–4.76)	2.32 (1.55–4.15)	0.485
VLF	797.19±290.75	934±330.33	1008.76±415.95	0.117*
T0‡	-3.19 (-1.66-{-8.75})	-2.1 (-1.57-{-2.65})	-2.95 (-1.56-{-4.88})	0.116
TS‡	16.55 (11.69–36.3)	13.8 (8.2–19.35)	13.67 (8.59–22.19)	0.426

HF; high frequency, LF; low frequency, pNN50; percentage of differences between adjacent NN intervals >50 msn, rMSSD; root mean square of the successive differences, SDANN; standard deviation of 5 min averaged NN intervals, SDNN; standard deviation of all NN intervals, T0; turbulence onset, TS; turbulence slope, VLF; very-low frequency. Data are shown as median (25 th-75th percentile) or mean ± standard deviation. Kruskal Wallis test (Post-Hoc: Dunn test), *: One-way analysis of variance, a, b, c: same letters indicate no significant difference between the groups; p>0.05, different letters indicate significant difference between the groups; p<0.05. ‡: Nephritic syndrome group: n=10, Nephrotic syndrome group: n=9, Healthy group: T0 n=41, TS n=43.

Table 5. *Effect of duration of glomerulonephritis on SDNN and rMSSD according to microalbuminuria level in 24-hour urine*

		Microalbuminuria in 24-hour urine			
	Total	<30 mg/day	30–300 mg/day	>300 mg/day	p
Number of patients, n (%)	42 (100)	10 (23.8)	9 (21.4)	23 (54.8)	
SDNN					
SDNN <141 msn, n (%)	30 (71.4)	6 (60.0)	7 (77.8)	17 (73.9)	
Median duration (95% CI), month	80 (65.8–92.2)	80 (8.8–151.1)	69 (33.7–104.3)	71 (51–91)	0.597
rMSSD					
rMSSD <27 msn, n (%)	26 (61.9)	5 (50)	5 (55.6)	16 (69.6)	
Median duration, month	80 (67.3–92.6)	80 (0–198.5)	85 (0–182.9)	80 (65.4–94.6)	0.483

CI: Confidence interval, rMSSD; root mean square of the successive differences, SDNN; standard deviation of all NN intervals.
The median time is based on the time from the diagnosis of chronic glomerulonephritis to the evaluation.

Analysis of the 24-hour ECG Holter results revealed that pNN50 and rMSSD values were significantly lower in the nephritic syndrome group compared to healthy subjects (p=0.049, p=0.032, respectively). In contrast, the significant differences in SDNN, SDNN index and HF were no longer observed. In the nephrotic syndrome group, the decrease in HRV parameters did not reach statistical significance compared to the healthy group (Table 4).

Analysis with Kaplan Meier Method in patients: Microalbuminuria levels were evaluated using patients' 24-hour urine samples. Among the patients, 23.8% (n=10) had normal/mild microalbuminuria (<30 mg/day), 21.4% (n=9) had moderate microalbuminuria (30–300 mg/day), and 54.8% (n=23) had severe microalbuminuria (>300 mg/day). The time from diagnosis to evaluation was calculated to determine the duration of CGN in each patient.

Heart rate variability parameters were categorized using pre-defined cut-off values: SDNN was dichotomized at 141 msec (with 71.4% of patients, n=30, having SDNN values below 141 msec) and rMSSD at 27 msec (with 61.9% of patients, n=26, having rMSSD values below 27 msec). The median duration from the diagnosis of chronic glomerulonephritis to the point at which SDNN and rMSSD fell to risky levels was compared according to the microalbuminuria levels in 24-hour urine samples.

In the analysis, no significant difference was observed among the microalbuminuria groups (based on 24-hour urine samples) regarding the duration from CGN diagnosis to the point at which SDNN fell below 141 msec, and rMSSD fell below 27 msec (Table 5, Figure 1).

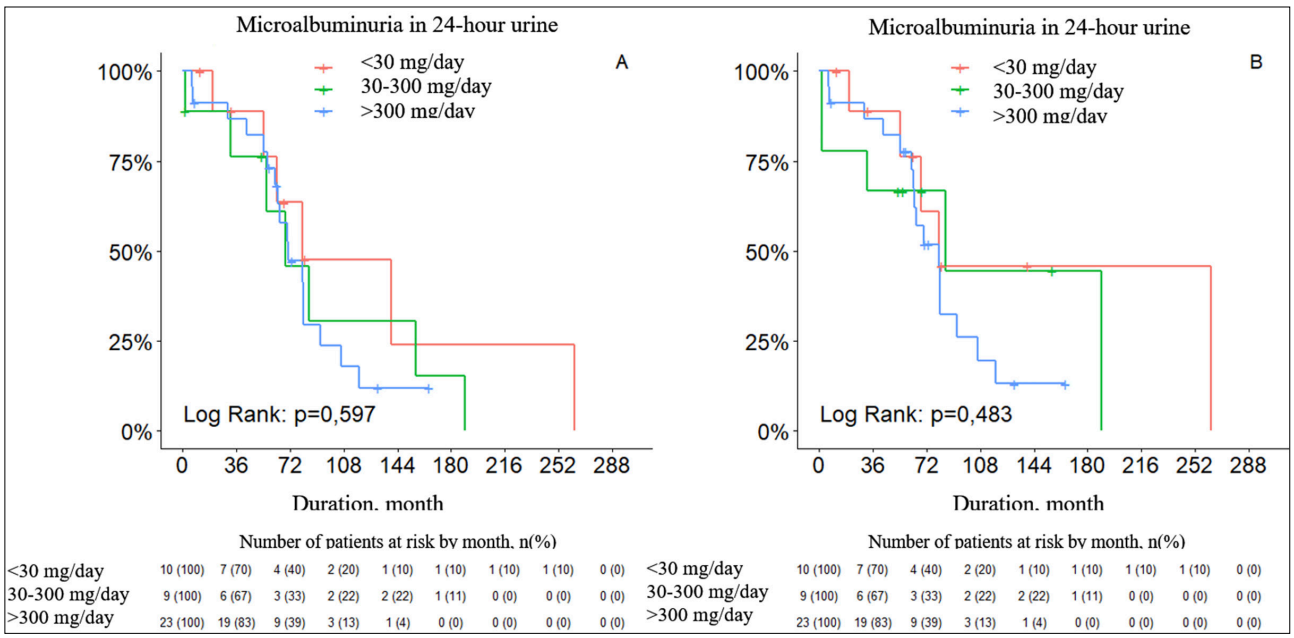

Figure 1. a,b. *Graphical presentation of the effect of glomerulonephritis duration on SDNN and rMSSD according to the microalbuminuria level in 24-hour urine.*

Discussion

This study evaluates cardiac autonomic function in the largest population of individuals with chronic glomerulonephritis before the onset of renal dysfunction. In this study, we found that the HRV parameters –SDNN, SDNN index, rMSSD, pNN50 and HF, which are important predictors of cardiac mortality– were significantly lower in the CGN group compared to the healthy group. These findings indicate the presence of autonomic dysfunction, marked by sympathetic activation and vagal suppression, even in CGN patients at the early stage. Since sympathetic-dominant autonomic dysfunction is associated with SCD, these results are crucial for the early prediction of CV risk and may guide timely intervention and treatment.

Our study found a statistically significant decrease in SDNN and the SDNN index in patients with CGN compared to control subjects (p=0.046 and p=0.031, respectively). In the study by Esposito et al.,[17] 21 patients with primary glomerulonephritis (without nephrotic syndrome) in the early stages of CKD were compared with 20 healthy subjects regarding time-domain HRV parameters. They found that SDNN was significantly lower in the patient group, which they interpreted as indicative of sympathetic hyperactivation and autonomic dysfunction. In this context, our findings regarding SDNN are consistent with those of Esposito et al. Moreover, the SDNN index –another parameter reflecting both short- and long-term influences on heart rate– was significantly lower in our patient group, further supporting the presence of sympathetic hyperactivation. However, when we divided the patient population into nephrotic and nephritic syndrome subgroups, the significant differences in SDNN and SDNN index observed in the overall patient group disappeared in both subgroups compared to the healthy group, contradicting the findings of Esposito et al., who evaluated CGN patients without nephrotic syndrome. This discrepancy may be due to the reduced sample size.

Both rMSSD and pNN50 were lower in the patient group, with these differences reaching statistical significance (p=0.019 and p=0.013, respectively), indicating a reduction in parasympathetic tone. In the subgroup analysis, when patients were divided into nephrotic and nephritic syndrome groups, rMSSD and pNN50 were lower in both subgroups compared to healthy controls; however, statistical significance was maintained only in the nephritic syndrome group, while it was lost in the nephrotic syndrome group. Although this discrepancy may be partly attributable to the small sample size, the persistence of a statistically significant difference in the nephritic syndrome group –despite its smaller number of patients– suggests that other factors may be involved. It is known that the correlation between glomerular filtration rate (GFR) and autonomic function is curvilinear[18]. Glomerular filtration rate was significantly lower in the nephritic

syndrome group compared to healthy subjects, unlike in the nephrotic syndrome group; it is plausible that the decreases in rMSSD and pNN50 are related to reduced GFR. Furthermore, the nephritic syndrome is characterized by inflammation and immune complex deposition[19], and inflammatory markers have been shown to correlate negatively with HRV parameters, particularly pNN50[20]. Therefore, we propose that inflammation in nephritic syndrome patients may be one of the reasons for the observed statistically significant differences in pNN50 and rMSSD. Unfortunately, we were unable to quantitatively assess this relationship via CRP levels due to changes in the CRP assay during the study period.

In our study, a comparison between the patient and control groups revealed that patients exhibited decreases in both LF and HF, along with an increase in the LF/HF ratio, reflecting sympathetic activation and parasympathetic inhibition. A statistically significant difference was observed for HF (p=0.032), indicating reduced vagal tone in the patient group. Andoh et al.[21] investigated HRV via power spectral analysis in patients with nephrotic syndrome in the early stages of CKD to assess the role of sympathetic withdrawal in reducing sleep blood pressure. They found no significant differences between groups in HF and LF/HF ratios. Although they did not attribute the absence of a decrease in sleep blood pressure to a direct sympathetic effect– since no autonomic dysfunction was detected in the HRV analysis –they suggested that sympathetic activity might still play a role, as indicated by a higher heart rate during sleep in the patient group. In our study of CGN patients, overall, we observed reduced vagal tone and a shift toward sympathetic dominance. However, when the patient group was divided into nephrotic and nephritic syndrome subgroups, the significant difference in HF observed in the overall group was no longer evident. Our findings in the nephrotic syndrome subgroup are consistent with those of Andoh et al.

Andoh et al. reported a negative correlation between serum albumin concentration (SAC) and urinary protein excretion, suggesting that SAC may serve as a proxy marker for the severity of nephrotic syndrome. In our study, although both nephritic and nephrotic syndrome subgroups had significantly lower serum total protein and albumin levels than the healthy group, no significant differences in HRV parameters were observed in the nephrotic syndrome subgroup relative to healthy controls. In contrast, the nephritic syndrome subgroup showed a significant decrease in rMSSD and pNN50 values compared to healthy subjects. Subsequently, we examined the effect of proteinuria levels in 24-hour urine –a more quantitative measure– on HRV parameters. Using the Kaplan–Meier method, we analyzed the time from CGN diagnosis to the point at which SDNN and rMSSD reached significantly reduced levels, stratified by microalbuminuria. Our findings indicate that microalbuminuria level (mild, moderate, or severe) does not significantly affect the mean duration of disease at which HRV parameters deteriorate (p=0.597 for SDNN and p=0.483 for rMSSD). However, while no linear relationship was observed for SDNN, the proportion of patients with reduced rMSSD increased with higher microalbuminuria levels. This underscores the impact of microalbuminuria on rMSSD, an independent risk factor for mortality in CKD patients[22].

Time-domain measurements of HRV, such as rMSSD and pNN50, are closely related to frequency-domain measurements, particularly the HF parameter[11]. In our study, the significant and concordant reductions in HF, rMSSD, and pNN50 observed in the patient group reinforce the conclusion that vagal tone is diminished in these patients.

Suitable VES were detected for analysis in 19 individuals (45%) in the patient group and 41 individuals (40%) in the healthy group. Analysis of these VES revealed no significant differences between the patient and healthy groups regarding TO and TS. According to our findings, HRT parameters –used as mortality predictors– do not appear to be sensitive markers for determining risk in CGN patients in the early stages of CKD. The fact that suitable VES were observed in only 41% of the individuals included in the study may have influenced these HRT results.

This study has several limitations. The most important is its small sample size –a common issue in HRT studies– which makes it difficult to identify appropriate VES. Furthermore, because the echocardiographic data for the healthy volunteer group were obtained retrospectively, not all subjects were evaluated by the same individual, potentially introducing interobserver variability. Additionally, as the study was conducted in the post-COVID-19 period –and previous studies have demonstrated that HRV is increased in symptomatic individuals who have recovered from COVID-19[23]– the lack of assessment of COVID-19

history and symptoms means that their impact on the results remains unclear. Lastly, although this study involved a larger population than previous studies in this field, further investigations with larger sample sizes are needed to obtain definitive data.

Conclusion

As a result, the HRV parameters SDNN, SDNN index, rMSSD, pNN50, and HF were significantly lower in the patient group compared to the healthy group. Based on our findings, we conclude that these parameters are reliable, practical, and non-invasive tests that can predict cardiovascular autonomic dysfunction in chronic glomerulonephritis patients at the early stages of chronic kidney disease.

References

1. Sethi S, De Vriese AS, Fervenza FC. Acute glomerulonephritis. The Lancet 2022, 399. 10335:1646–1663.
2. Dickinson BL. Unraveling the immunopathogenesis of glomerular disease. Clin Immunol. 2016;169:89–97.
3. Öztürk S. Primer Glomerüler Hastalıkların Tanı ve Tedavisi: Türk Nefroloji Derneği Ulusal Uzlaşı Raporu. 2019:29–35.
4. Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100(4):1–276.
5. O'brien I, McFadden J, Corrall R. The influence of autonomic neuropathy on mortality in insulin-dependent diabetes. An Int J Med. 1991;79(3):495–502.
6. Schmidt G, Malik M, Barthel P, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet. 1999;353(9162):1390–6.
7. Chandra P, Sands RL, Gillespie BW, et al. Predictors of heart rate variability and its prognostic significance in chronic kidney disease. Nephrol Dial Transplant. 2012;27(2):700–9.
8. Braunisch MC, Mayer CC, Bauer A, et al. Cardiovascular mortality can be predicted by heart rate turbulence in hemodialysis patients. Frontiers Physiol. 2020;11:77.
9. Gamal E, Behairy MA, Mohammed ME, Ahmed EY, Abdel Rahman Ahmed MD. A Study of Cardiac Autonomic Neuropathy among Non-Diabetic Chronic Kidney Disease Patients. The Medical Journal of Cairo University, 2022, 90. 12:2263–2275.
10. Candemir M, Sezenöz B, & Özdemir M. Predictors of Paroxysmal Atrial Fibrillation: Heart Rate Variability and Heart Rate Turbulence. Kafkas Journal of Medical Sciences, 2022, 12(1), 65–70.
11. Kleiger RE, Bigger JT, Bosner MS, et al. Stability over time of variables measuring heart rate variability in normal subjects. Am J Cardiol. 1991;68(6):626–30.
12. Kamath MV, Ghista DN, Fallen EL, Fitchett D, Miller D, McKelvie R. Heart rate variability power spectrogram as a potential noninvasive signature of cardiac regulatory system response, mechanisms, and disorders. Heart Vessels. 1987;3(1):33 41.
13. Lombardi F, Ruscone TG, Malliani A. Premature ventricular contractions and reflex sympathetic activation in cats. Cardiovasc Res. 1989;23(3):205–12.
14. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996;93(5):1043–65.
15. Watanabe MA. Heart rate turbulence: a review. Indian Pacing Electrophysiol J. 2003;3(1):10.
16. Cygankiewicz I. Heart rate turbulence. Progress Cardiovasc Dis. 2013;56(2):160–71.
17. Esposito P, Palmieri V, Migliaresi P, Pezzullo S, Martino S, Balletta MM. Preclinical cardiovascular abnormalities in patients in early stages of renal disease without nephrotic syndrome. Hypertens Res. 2009;32(12):1155–6.
18. Clyne N, Hellberg M, Kouidi E, Deligiannis A, Höglund P. Relationship between declining glomerular filtration rate and measures of cardiac and vascular autonomic neuropathy. Nephrology. 2016;21(12):1047–55.
19. Hashmi MS, Pandey J. Nephritic Syndrome. 2022 Aug 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;2022. PMID:32965911.
20. Haensel A, Mills PJ, Nelesen RA, Ziegler MG, Dimsdale JE. The relationship between heart rate variability and inflammatory markers in cardiovascular diseases. Psychoneuroendocrinology. 2008;33(10):1305–12.
21. Andoh D, Kobayashi M, Yasuda G, et al. Loss of nocturnal decline of blood pressure in non-diabetic patients with nephrotic syndrome in the early and middle stages of chronic kidney disease. Hypertension Res. 2009;32(5):364–8.
22. Drawz PE, Babineau DC, Brecklin C, et al. Heart rate variability is a predictor of mortality in chronic kidney disease: a report from the CRIC Study. Am J Nephrol. 2013;38(6):517–28.
23. Karakayalı M, Artac I, Ilis D, et al. Evaluation of outpatients in the post-COVID-19 period in terms of autonomic dysfunction and silent ischemia. Cureus, 2023, 15(6).

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Blood Viscosity and the Other Laboratory Parameters as Diagnostic Determinants of Pulmonary Embolism

Pulmoner Embolide Tanısal Belirleyici Olarak Tam Kan Viskositesi ve Diğer Laboratuvar Parametreleri

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ABSTRACT

Aim: *Pulmonary embolism (PE) is a significant cardiovascular condition and a leading cause of mortality worldwide. Diagnosing PE remains challenging due to nonspecific symptoms and limited accessible laboratory tests beyond D-dimer. This retrospective study aimed to evaluate the predictive properties of blood parameters, particularly whole blood viscosity (WBV), for early PE diagnosis.*

Material and Methods: *The study included 72 patients with acute PE and 72 age and sex-matched controls. Data regarding past illnesses, blood tests, and basic echocardiography findings of all patients were obtained. Whole blood viscosity was assessed at low shear rate (LSR) and high shear rate (HSR) using established formulas incorporating hematocrit and total plasma protein.*

Results: *Significant differences were observed in various laboratory parameters between the groups. Whole blood viscosity at both LSR and HSR was significantly higher in the PE group than in controls (p <0.005). Receiver operating characteristic (ROC) analysis demonstrated strong diagnostic capability for WBV, with high specificity and positive predictive value. The optimal cut-off values for WBV at LSR and HSR were ≥4.20 and ≥27.22, respectively. Correlation analyses revealed a significant positive relationship between WBV and pulmonary arterial pressure.*

Conclusions: *The findings suggest that WBV, which can be calculated using routine laboratory parameters, holds potential as a diagnostic tool for PE. Integrating WBV assessment could enhance the accuracy and efficiency of PE diagnosis, potentially reducing the need for invasive or radiation-exposing procedures. Further research is necessary to validate these findings in larger populations and establish standardized cut-off values for clinical application.*

Key words: *blood viscosity; pulmonary embolism; venous thromboembolism; hypercoagulability; shear rate*

ÖZET

Amaç: *Pulmoner emboli (PE) önemli bir kardiyovasküler hastalıktır ve dünya çapında önde gelen ölüm nedenlerinden biridir. Pulmoner emboli tanısı, nonspesifik semptomlar ve D-dimer dışında erişilebilir laboratuvar testlerinin sınırlı olması nedeniyle zorlu olmaya devam etmektedir. Bu retrospektif çalışma, erken PE tanısı için kan parametrelerinin, özellikle tam kan viskozitesinin (WBV) öngördürücü özelliklerini değerlendirmeyi amaçlamaktadır.*

Gereç ve Yöntem: *Çalışmaya akut PE tanısı almış olan 72 hasta ve 72 benzer yaş ve cinsiyet özelliklerine sahip gönüllü dâhil edildi. Tüm katılımcıların geçmiş hastalıkları, kan testleri ve temel ekokardiyografi bulgularına ilişkin veriler kaydedildi. WBV, hematokrit ve toplam plazma proteinini içeren yerleşik formüller kullanılarak düşük shear rate (LSR) ve yüksek shear rate (HSR) değerlerinde incelendi.*

Bulgular: *Gruplar arasında çeşitli laboratuvar parametrelerinde önemli farklılıklar gözlendi. Hem LSR hem de HSR'deki WBV, PE grubunda kontrollerle karşılaştırıldığında önemli ölçüde daha yüksekti (p <0,005). Alıcı işletim karakteristiği (ROC) analizi, WBV'in yüksek özgüllük ve pozitif öngörücü değere sahip olduğunu ve güçlü tanısal kapasite gösterdiğini saptadı. Düşük shear rate ve HSR'de WBV için optimum cut-off değerleri sırasıyla ≥4,20 ve ≥27,22 idi. Korelasyon analizleri WBV ile pulmoner arter basıncı arasında önemli bir pozitif ilişki olduğunu ortaya koydu.*

Sonuç: *Bulgular, rutin laboratuvar parametreleri kullanılarak hesaplanabilen WBV'nin PE için değerli bir tanı aracı olarak kullanılabileceğini göstermektedir. Tam kan viskozitesi (WBV) sonuçlarının tanı algoritmasına eklenmesi, PE tanısının doğruluğunu ve verimliliğini artırabilir; böylece invaziv veya radyasyona maruz bırakan prosedürlere olan ihtiyacı azaltabilir. Bu yeni tekniğin klinik kullanıma geçebilmesi için bulguların daha geniş popülasyonlarda doğrulanması ve klinik uygulama için standart cut-off değerlerinin belirlenmesi gereklidir.*

Anahtar kelimeler: *kan viskositesi; pulmoner emboli; venöz tromboemboli; hiperkoagülabilite; shear rate*

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Introduction

Pulmonary Embolism (PE) is a significant cardiovascular condition, ranking as the third most common cause of cardiovascular death worldwide, after stroke and heart attack. The exact prevalence of Venous Thromboembolism (VTE), which includes PE and Deep Vein Thrombosis (DVT), is challenging to determine because of the wide range of nonspecific presenting signs and symptoms. It is shown that for every nonfatal PE, 2.5 PE cases are diagnosed at autopsy[1]. In the United States, the annual incidence of VTE is estimated to be between 300.000 and 600.000. Necroscopic studies indicate that PE accounts for approximately 5%–10% of deaths in hospitalized patients. The mortality rate of untreated PE can reach up to 25%; however, with appropriate treatment, it decreases to 1–5%[2]. The pathophysiology of VTE, as described by Virchow in the 19th century, involves three key factors: stasis, endothelial disruption, and hypercoagulability[3].

Diagnosing PE can be challenging because of nonspecific symptoms. The common presenting symptoms include pleuritic chest pain (39%), dyspnea at rest (50%), hemoptysis (up to 20%), and syncope (in hemodynamically significant PE). A thorough evaluation of the risk factors and clinical presentation is essential for accurate diagnosis. The diagnostic process often involves clinical assessment, laboratory tests, and imaging studies. D-dimer testing is frequently used as an initial screening tool, with elevated levels suggesting the need for further investigation. Computed tomography pulmonary angiography (CTPA) is considered the gold standard for confirming PE, providing detailed images of the pulmonary vasculature and enabling the visualization of emboli. Echocardiography can be valuable in assessing right ventricular function and identifying signs of right heart strain, which may indicate more severe PE. Early recognition and prompt treatment are crucial for improving the outcomes of patients with PE[4,5].

Venous thrombosis is primarily attributed to three key factors: endothelial injury, hemodynamic alterations, and hypercoagulability. This pathological condition arises from modifications in the blood flow dynamics and viscosity, with hyperviscosity playing a particularly significant role[6]. Moreover, elevated shear stress associated with hyperviscosity leads to endothelial damage and subsequent thrombosis. Blood is a non-Newtonian fluid, and its viscosity varies with shear rate. Red blood cells (RBCs) tend to aggregate at low shear rates and significantly increase viscosity[7]. Conversely, at higher shear rates, RBCs disaggregate, deform, and align with the flow direction, reducing viscosity. The primary determinants of blood viscosity include hematocrit, plasma macromolecules, and RBC deformability[8]. This phenomenon of RBC behavior at different shear rates is known as shear thinning, a key characteristic of blood rheology. The interplay between these determinants of blood viscosity can significantly impact blood flow dynamics, especially in the microcirculation. Whole blood viscosity has been found to predict future cardiovascular events in the short and long term. The relationship between blood viscosity and cardiovascular risk underscores the importance of hemorheological factors in vascular health and disease progression[9,10].

Apart from the D-dimer test, the lack of easily accessible, fast-yielding, and low-cost laboratory tests to help diagnose PE makes the diagnosis difficult and sometimes leads to failure to diagnose PE. In this study, we aimed to evaluate the predictive properties of blood parameters, especially whole blood viscosity, which can be calculated through routine laboratory examinations for the early diagnosis of PE.

Material and Methods

Patients and Study Design

Patients diagnosed with acute pulmonary embolism at Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital between 01.01.2022 and 01.01.2024 were included in our retrospective study. The criterion for definitive diagnosis of acute pulmonary embolism was determined as the detection of embolism in the pulmonary arteries on computed tomographic angiography, which is considered the gold standard for diagnosis. All patients diagnosed with acute pulmonary embolism within the specified criteria between the specified dates were scanned from our hospital's electronic record system, and all patients who met the exclusion and inclusion criteria were included in the study. Exclusion criteria were determined as known malignancy history, previous deep vein thrombosis (DVT) or pulmonary thromboembolism (PTE), known genetic or acquired coagulation disorder, heart failure diagnosis, recent trauma or major surgery history, long-term immobility, and the patient is under 18 or over 75 years of age. A hundred and sixty six patients diagnosed with pulmonary embolism within the specified dates were evaluated, and the remaining 72 patients were included in the study after the exclusion

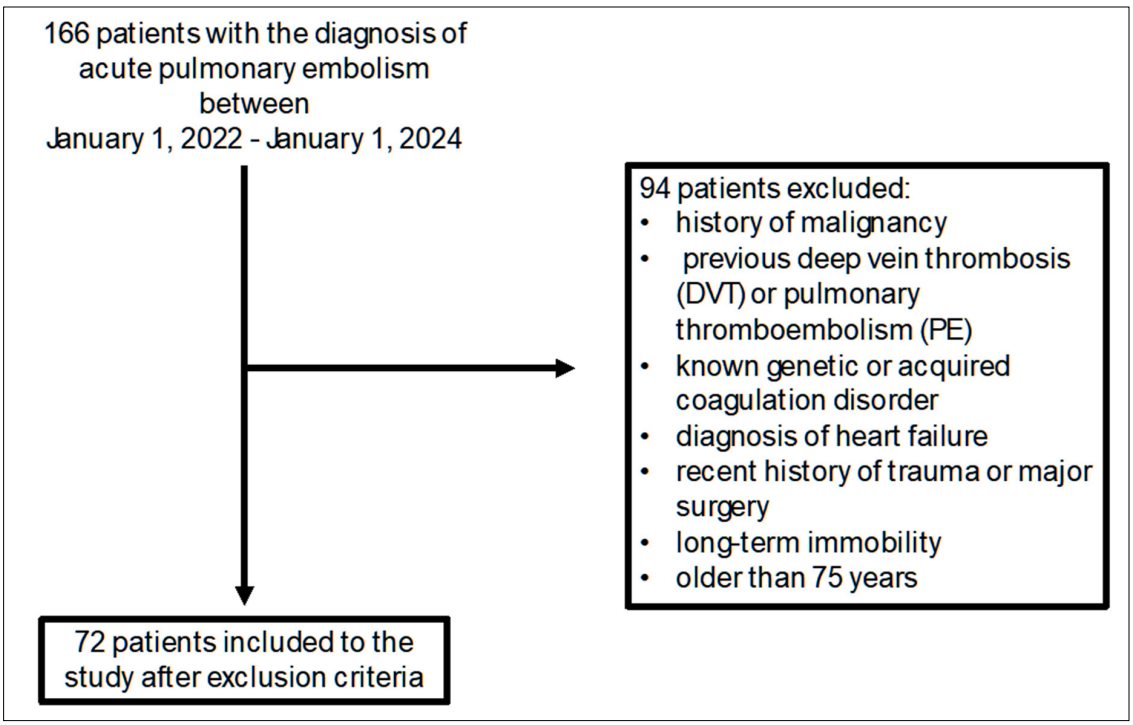


Figure 1. *Flow chart showing the patient selection process.*

criteria were applied (Figure 1). The control group was selected from patients who applied to our outpatient clinic and had age and sex characteristics similar to those of the study group by following the same exclusion criteria. Data regarding past illnesses, blood tests, and basic echocardiography findings of all patients included in the study were obtained from our hospital's electronic record system and compared. The laboratory parameters on the date when the patients were admitted to the emergency department and diagnosed with acute pulmonary thromboembolism were used.

The study was approved by the ethics committee of the Amasya University Rectorate Non-Interventional Clinical Research Ethics Committee on 03.10.2024 under the approval number 2024000099–1.

Whole blood viscosity

Whole blood viscosity (WBV) was assessed at both high shear rate (HSR=208/s) and low shear rate (LSR=0.5/s), employing established formulas that integrate hematocrit and total plasma protein concentration measurements.

The formula for WBV at HSR (208/s) is expressed as: (0.12* Hct) + (0.17* [TP-2.07])

And for LSR, WBV (0.5/s) is calculated using: (1.89* Hct) + (3.76* [TP-78.42])

In these equations, Hct represents hematocrit (%), TP denotes total protein concentration (g/L), and WBV is measured in centipoise (cP)[11].

Statistical Analysis

The research data were entered and analyzed using the IBM Statistical Package for Social Sciences (SPSS) for Windows program version 22.0 software (IBM Inc., Chicago, IL). Descriptive statistics were presented as median (Q1-Q3), frequency distributions, and percentages.

The Pearson Chi-Square Test, Fisher's Exact Test, and McNemar Test were employed to evaluate categorical variables. Variable distributions' normality was assessed using visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov Test/Shapiro-Wilk Test).

For variables that did not conform to a normal distribution, the Mann-Whitney U Test was used to determine statistical significance between two independent groups. The diagnostic ability of WBV at LSR and WBV at HSR to predict pulmonary embolism was evaluated using Receiver Operating Characteristic (ROC) curve analysis. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for significant threshold values.

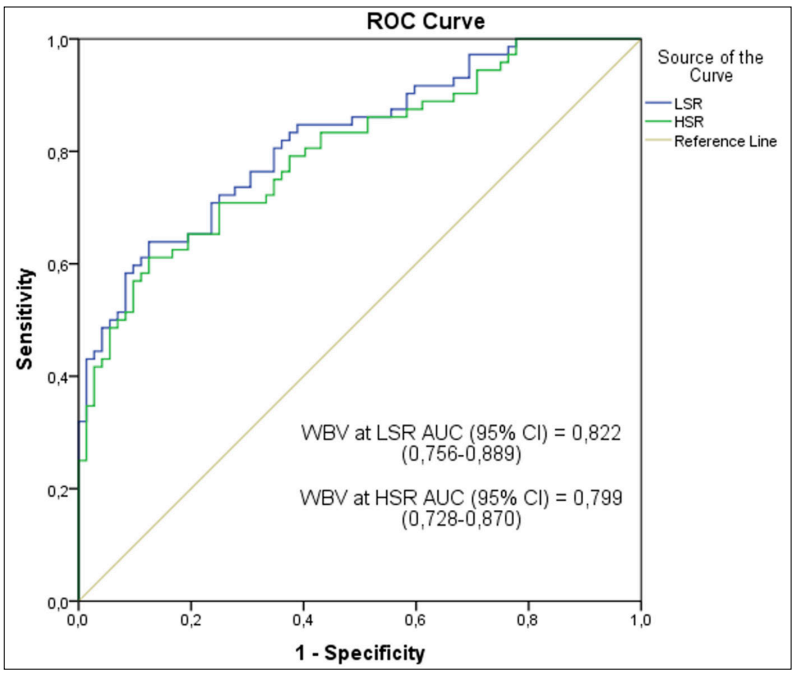


Figure 2. *ROC Analysis Results for Whole Blood Viscosity (WBV) at Low Shear Rate (LSR) and High Shear Rate (HSR).*

The relationships between variables were analyzed using Spearman's Correlation Test. A p-value of <0.05 was considered statistically significant.

Results

The study included 72 patients in the pulmonary embolism (PE) group and 72 in the control group. Baseline demographic characteristics and laboratory findings are summarized in Table 1. No significant differences were observed between the groups regarding age, gender distribution, or comorbidities such as diabetes mellitus, hypertension, chronic kidney disease, and coronary artery disease (all p >0.05).

Significant differences were noted in laboratory parameters. White blood cell (WBC) counts were markedly higher in the PE group compared to controls (11.2 [8–13.1] × 10^3/μL vs. 6.6 [5.3–7.9] × 10^3/μL, p <0.005). Additionally, hematocrit, blood glucose, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, and C-reactive protein (CRP) levels were significantly elevated in the PE group. In contrast, serum albumin levels were lower (all p <0.005).

Whole blood viscosity (WBV) was assessed at both low shear rate (LSR) and high shear rate (HSR), revealing significantly higher values in the PE group (4.4 [3.9–4.7] vs. 3.8 [3.6–4.0] for WBV at LSR and 30.6 [22.4–35.3] vs. 20.5 [17.7–23.7] for WBV at HSR, p <0.005 for both). The echocardiographic evaluation showed that the PE group's pulmonary arterial pressure (sPAB) and right ventricular (RV) diameter were significantly greater. In contrast, left ventricular ejection fraction (LVEF) was slightly reduced (all p <0.005).

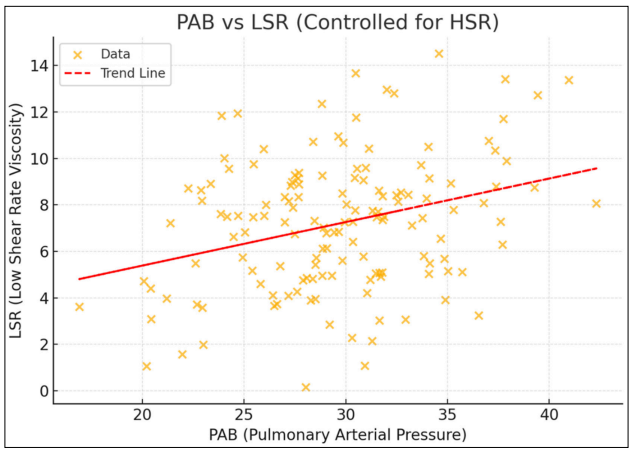
Table 2 presents the diagnostic performance metrics of WBV at LSR and HSR for detecting PE. The ROC analysis demonstrated strong diagnostic capability for both WBV parameters (Figure 2).

For WBV at LSR, the area under the curve (AUC) was 0.822 (95% CI: 0.756–0.889), indicating excellent diagnostic discrimination. A cut-off value of ≥4.20 was identified, achieving a sensitivity of 63.89% (95% CI: 51.71–74.88) and a specificity of 87.5% (95% CI: 77.59–94.12). The positive predictive value (PPV) was 83.64% (95% CI:

Table 2. *Results of whole blood viscosity at low shear rate (LSR) and high shear rate (HSR) in patients with pulmonary thromboembolism*

	WBV at LSR	WBV at HSR
Cut-off value	≥27.22	≥4.20
AUC (95% CI)	0.822 (0.756–0.889)	0.799 (0.728–0.870)
Sensitivity	63.89 (51.71–74.88)	61.11 (48.89–72.38)
Specificity	87.5 (77.59–94.12)	87.5 (77.59–94.12)
Positive predictive value	83.64 (73.03–90.61)	83.02 (72.08–90.25)
Negative predictive value	70.79 (63.78–76.93)	69.23 (62.45–75.28)
Accuracy	75.69 (67.85–82.45)	74.31 (66.36–81.22)

AUC: area under curve, CI: confidence interval.



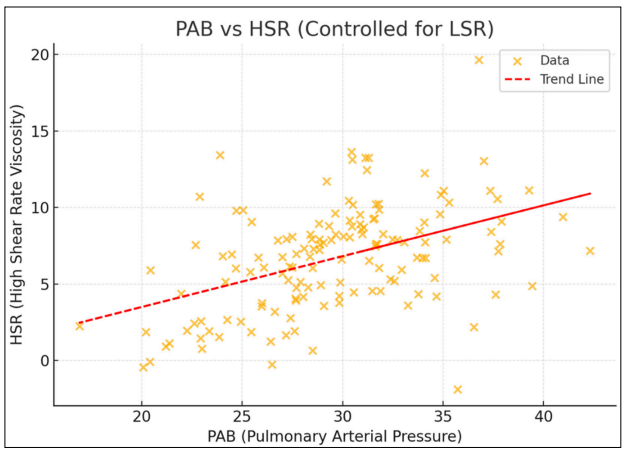


Figure 3. a–b. *Scatter plot illustrating the positive relationship between sPAB (Pulmonary Arterial Pressure) and LSR (Low Shear Rate Viscosity) after controlling for HSR (High Shear Rate Viscosity). The red dashed line represents the trend line (r=0.233, p=0.005)* **(a).** *Scatter plot showing the positive relationship between sPAB (Pulmonary Arterial Pressure) and HSR (High Shear Rate Viscosity) after controlling for LSR (Low Shear Rate Viscosity). The red dashed line highlights the trend (r=0.220, p=0.008)* **(b)**.

Table 1. *Baseline demographic characteristics and the laboratory parameters of the patients*

	Pulmonary Embolism Group (n=72)	Control Group (n=72)	p value
Female, n (%)	41 (56.9%)	43 (59.7%)	0.735
Age	65 (54–69)	59 (51–69.8)	0.195
DM, n (%)	25 (34.7%)	24 (33.3%)	0.860
HT, n (%)	29 (40.2%)	27 (37.5%)	0.732
Chronic kidney disease, n (%)	1 (1.38%)	2 (2.77%)	0.500
Coronary artery disease, n (%)	12 (16.6%)	11 (15.2%)	1.000
WBC (10^3/uL)	11.2 (8–13,1)	6.6 (5,3–7,9)	<0.005
Hemoglobin (g/dl)	13.6 (12.7–14.6)	13.5 (12.7–14.1)	0.363
Hematocrit (%)	43.4 (39.4–45.7)	39.4 (38.1–41.6)	**<0.005**
Platelet count (10^3/uL)	241 (195–297)	216 (193–262)	0.076
Blood glucose (mg/dl)	136.5 (103–194.8)	100 (95–111)	**<0.005**
Creatinine (mg/dl)	0.9 (0.8–1)	0.7 (0.6–0.9)	<0.005
AST (U/l)	27 (19–41)	20 (17–24)	**<0.005**
ALT (U/l)	20 (14–34)	16.5 (13.3–23)	**<0.005**
Total protein (g/dl)	7.1 (6.8–7.6)	6.5 (6.2–6.7)	**<0.005**
Albumin (g/dl)	3.9 (3.7–4.3)	4.2 (4–4.3)	**0.004**
CRP (mg/dl)	37.8 (21–67,1)	2.8 (1,2–4,4)	**<0.005**
Troponin positive at admission, n (%)	28 (38.8%)	N/A	
WBV at LSR	4.4 (3.9–4.7)	3.8 (3.6–4)	**<0.005**
WBV at HSR	30.6 (22.4–35.3)	20.5 (17.7–23.7)	**<0.005**
Echocardiographic parameters			
LVEF (%)	60 (55–60)	60 (60–65)	**<0.005**
sPAB (mmHg)	30 (25–45)	20 (15–20)	**<0.005**
RV diameter (mm)	32 (29–36.8)	30 (28–30)	**<0.005**

Non-categorical data are presented as Median (Q1-Q3). DM: diabetes mellitus, HT: hypertension, WBC: white blood cell count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, WBV at LSR: whole blood viscosity at low shear rate, WBV at HSR: whole blood viscosity at high shear rate, LVEF: left ventricular ejection fraction, sPAB: pulmonary arterial pressure, RV: right ventricle.

73.03–90.61), while the negative predictive value (NPV) was 70.79% (95% CI: 63.78–76.93). The overall diagnostic accuracy for WBV at LSR was 75.69% (95% CI: 67.85–82.45).

Similarly, WBV at HSR demonstrated an AUC of 0.799 (95% CI: 0.728–0.870), reflecting a robust ability to differentiate PE patients from controls. The optimal cut-off value was ≥27.22, with a sensitivity of 61.11% (95% CI: 48.89–72.38) and a specificity of 87.5% (95% CI: 77.59–94.12). The PPV for WBV at HSR was 83.02% (95% CI: 72.08–90.25), and the NPV was 69.23% (95% CI: 62.45–75.28). The diagnostic accuracy was calculated at 74.31% (95% CI: 66.36–81.22).

Correlation analyses (Table 3, Figures 3A and 3B) revealed a significant positive relationship between WBV and sPAB. Spearman correlation coefficients indicated moderate correlations for both WBV at LSR (r=0.319, p <0.005) and WBV at HSR (r=0.294, p <0.005). After controlling for covariates, partial correlation analysis confirmed the persistence of this relationship for WBV at LSR (r=0.233, p=0.005) and WBV at HSR (r=0.220, p=0.008).

Table 3. *Investigation of the relationship between pulmonary artery pressure (PAB) and whole blood viscosity at low shear rate (LSR) and high shear rate (HSR)*

	sPAB			
	r_1	p	r_2	p
WBV at LSR	0.319	<0.005	0.233	**0.005**
WBV at HSR	0.294	<0.005	0.220	**0.008**

r_1:Spearman Correlation, r_2:partial correlation, p: p-value.

These findings highlight that WBV at both LSR and HSR are reliable indicators for diagnosing PE, with high specificity in distinguishing PE patients from controls. While the sensitivity values indicate moderate capability, the high PPV suggests that elevated WBV measurements strongly correlate with the presence of PE, making it a valuable diagnostic tool in clinical practice.

Discussion

The findings of our investigation demonstrate a significant increase in whole blood viscosity (WBV) under high and low shear stress, as measured using standard laboratory parameters, among patients with acute pulmonary embolism. The ROC analysis revealed a strong diagnostic capability with a high positive predictive value of these parameters to detect PE. There was also a strong positive correlation between WBV and sPAB values. Our research aimed to demonstrate that WBV measurement could serve as a valuable diagnostic tool for this condition, which often presents with a broad spectrum of nonspecific symptoms and signs and remains challenging to diagnose without specific laboratory tests beyond D-dimer. This study is among the first to systematically evaluate WBV changes in PE patients, highlighting a novel diagnostic avenue.

Pulmonary embolism diagnostic approaches have evolved significantly, reducing the need for invasive procedures. Modern algorithms use a sequential strategy combining pre-test probability assessment, D-dimer measurement, and chest imaging as necessary, optimizing the process while minimizing unnecessary tests and radiation exposure[12]. Using validated tools like the Wells and Geneva scores, clinical probability assessment is crucial in categorizing patients into low, intermediate, or high-risk groups based on clinical factors such as patient history and physical examination. D-dimer testing, which measures fibrin degradation products indicative of blood clots, is highly sensitive but not specific, requiring further investigation if positive[13,14]. When imaging is required, computed tomography pulmonary angiography is the primary diagnostic tool due to its high sensitivity and specificity for detecting pulmonary emboli. However, it involves radiation exposure and potential contrast-induced nephropathy[15]. Future advancements should focus on refining risk stratification tools, exploring new biomarkers to complement or replace D-dimer testing, and optimizing imaging techniques to reduce radiation exposure and enhance diagnostic accuracy, ultimately improving patient outcomes and healthcare efficiency[16].

The composition of blood determines its viscosity (BV), which demonstrates non-Newtonian fluid properties and changes with shear rate. Blood viscosity is influenced by various rheological factors, with blood cells and plasma components being key contributors. When BV increases, it results in decreased blood flow and subsequent stagnation. The complex effects of elevated BV accelerate atherothrombotic processes and the progression of cardiovascular disease, possibly impacting disease outcomes[17,18].

Technical requirements and a lack of standardized protocols limit the routine clinical measurement of whole blood viscosity using viscometers. De Simone et al. introduced a method to estimate WBV from hematocrit and total plasma protein at specific shear rates[11]. This formula uses different shear rates to represent various hemodynamic conditions: low shear rate (LSR) signifies end-diastolic low-velocity blood flow. In contrast, high shear rate (HSR) represents systolic peak high-velocity flow. The accuracy of this formula has been confirmed in large patient cohorts and through viscometer-based studies, and it has been utilized in various patient populations[19,20].

In a study that included 33 PE patients and 36 healthy controls, blood viscosity was measured with a special type of viscometer. The findings revealed significantly elevated mean plasma viscosity levels in PE patients. Additionally, significant differences were observed in fibrinogen, triglyceride, and hematocrit levels between PE patients and controls[21]. Also, in another study, Carlisi et al. found that elevated blood viscosity was associated with an increased risk of venous thromboembolism in their study of newly diagnosed Multiple Myeloma patients[22].

Pulmonary embolism, an acute inflammatory process, is associated with an expected increase in inflammation-related markers. Indeed, studies have corroborated this hypothesis[23,24]. For instance, in a study conducted by Köse et al. to evaluate neutrophil-lymphocyte (NLR), platelet-lymphocyte (PLR), and lymphocyte-monocyte (LMR) ratios in pulmonary embolism patients, markers such as WBC, platelet, and CRP were also found to be elevated, suggesting that these markers may be valuable in the diagnostic evaluation of PE[25]. In a cohort study conducted by Salinger-Martinovic et

al., hemodynamic deterioration resulting from acute pulmonary embolism was evaluated for its potential to induce multi-organ dysfunction. The investigation also revealed that progressive decline in renal function tests was associated with high mortality (26). Consistent with prior investigations, our findings revealed that individuals diagnosed with pulmonary embolism displayed markedly elevated levels of creatinine, WBC, CRP, AST, and ALT compared to the control group.

Limitations

The primary limitation arises from its retrospective methodology, which considerably restricted the scope of analyzable parameters. Although the dataset's completeness was satisfactory, incorporating additional variables could influence the final estimation models. Moreover, the study's restricted sample size presents an additional challenge. Another limitation of our study is that it is a single-center study. An expanded participant pool would enhance the statistical power of the analyses, particularly about regression techniques.

Conclusion

This study demonstrates that whole blood viscosity (WBV) at both low and high shear rates is significantly elevated in acute pulmonary embolism (PE) patients compared to controls. Receiver operating characteristic (ROC) analysis shows WBV has excellent discrimination ability, with high specificity and positive predictive value for PE detection. The correlation between WBV and pulmonary arterial pressure supports its potential as a valuable diagnostic tool.

The findings suggest that WBV measurement, calculable using routine laboratory parameters, may be a useful adjunct in diagnosing PE and addressing challenges due to its nonspecific presentation and current diagnostic limitations. While D-dimer and imaging remain crucial, integrating WBV assessment could enhance PE diagnosis accuracy and efficiency. The simplicity and accessibility of WBV calculation make it a practical option, potentially reducing the need for invasive or radiation-exposing procedures.

Further research is necessary to validate these findings in larger, diverse populations and establish standardized cut-off values. Prospective studies should also evaluate WBV's role in risk stratification and its potential to guide treatment decisions in PE management.

This study highlights WBV as a promising biomarker in PE diagnosis, suggesting new avenues for improving diagnostic approaches to this critical cardiovascular condition.

Disclosures

The principles of the Declaration of Helsinki conducted this study.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

The author declares no conflicts of interest.

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References

1. Tomkiewicz EM, Kline JA. Concise Review of the Clinical Approach to the Exclusion and Diagnosis of Pulmonary Embolism in 2020. J Emerg Nurs. 2020;46(4):527–38.
2. Konstantinides S V. Diagnosis of pulmonary embolism: progress after many years. The Lancet. 2017;390(10091):210–1.
3. Righini M, Le Gal G, Bounameaux H. Venous thromboembolism diagnosis: Unresolved issues. Thromb Haemost. 2015;113(6):1184–92.
4. Righini M, Robert-Ebadi H, Le Gal G. Diagnosis of acute pulmonary embolism. Journal of Thrombosis and Haemostasis. 2017;15(7):1251–61.
5. Cohen AT, Dobromirski M, Gurwith MMP. Managing pulmonary embolism from presentation to extended treatment. Thromb Res. 2014;133(2):139–48.
6. Stoltz JF, Donner M. New trends in clinical hemorheology: an introduction to the concept of the hemorheological profile. Schweiz Med Wochenschr Suppl. 1991;43:41–9.
7. Xiong X, Li T, Yu S, Cheng B. Association Between Red Blood Cell Indices and Preoperative Deep Vein Thrombosis in Patients Undergoing Total Joint Arthroplasty: A Retrospective Study. Clinical and Applied Thrombosis/Hemostasis. 2022;28.
8. Baskurt OK, Meiselman HJ. Blood Rheology and Hemodynamics. Semin Thromb Hemost. 2003;29(5):435–50.
9. Vayá A, Suescun M. Hemorheological parameters as independent predictors of venous thromboembolism. Clin Hemorheol Microcirc. 2013 [cited. 2025;53(1-2):131–41.

10. Lowe GDO, Rumley A, Whincup PH, Danesh J. Hemostatic and rheological variables and risk of cardiovascular disease. Semin Vasc Med. 2002;2(4):429–39.
11. De Simone G, Devereux RB, Chien S, Alderman MH, Atlas SA, Laragh JH. Relation of blood viscosity to demographic and physiologic variables and to cardiovascular risk factors in apparently normal adults. Circulation. 1990;81(1):107–17.
12. Van Belle A, Büller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA. 2006;295(2):172–9.
13. Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuysen A, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: The ADJUST-PE study. JAMA. 2014;311(11):1117–24.
14. Van der Hulle T, den Exter PL, Erkens PGM, van Es J, Mos ICM, ten Cate H, et al. Variable D-dimer thresholds for diagnosis of clinically suspected acute pulmonary embolism. Journal of Thrombosis and Haemostasis. 2013;11(11):1986–92.
15. Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD. Evaluation of patients with suspected acute pulmonary embolism: Best practice advice from the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2015;163(9):701–11.
16. van der Hulle T, Cheung WY, Kooij S, Beenen LFM, van Bemmel T, van Es J, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study) : a prospective, multicentre, cohort study. Lancet. 2017;390(10091):289–97.
17. Nwose EU. Cardiovascular risk assessment and support techniques. Whole blood viscosity assessment issues I. Extrapolation chart and reference values. N Am J Med Sci. 2010;2(4):165–9.
18. Pop GAM, Duncker DJ, Gardien M, Vranckx P, Versluis S, Hasan D, et al. The clinical significance of whole blood viscosity in (cardio) vascular medicine. Neth Heart J. 2002;10(12):512–6.
19. Uzunget SB, Sahin KE. Another possible determinant for ischemic stroke with nonvalvular atrial fibrillation other than conventional oral anticoagulant treatment: The relationship between whole blood viscosity and stroke. J Stroke Cerebrovasc Dis. 2022;31(9).
20. Cetin EHO, Cetin MS, Canpolat U, Aydin S, Aras D, Topaloglu S, et al. Prognostic significance of whole blood viscosity estimated by de Simone's formula in ST-elevation myocardial infarction. Biomark Med. 2016;10(5):495–511.
21. Atici AG, Kayhan S, Aydin D, Yilmaz YA. Plasma viscosity levels in pulmonary thromboembolism. Clin Hemorheol Microcirc. 2013;55(3):313–20.
22. Carlisi M, Presti R Lo, Mancuso S, Siragusa S, Caimi G. Thrombotic Risk and Calculated Whole Blood Viscosity in a Cohort of Patients With New Diagnosis of Multiple Myeloma. Clin Appl Thromb Hemost. 2024;30.
23. Abul Y, Karakurt S, Ozben B, Toprak A, Celikel T. C-reactive protein in acute pulmonary embolism. Journal of Investigative Medicine. 2011;59(1):8–14.
24. Afzal A, Noor HA, Gill SA, Brawncr C, Stein PD. Leukocytosis in acute pulmonary embolism. Chest. 1999;115(5):1329–32.
25. Köse N, Yıldırım T, Akın F, Yıldırım SE, Altun İ. Prognostic role of NLR, PLR, and LMR in patients with pulmonary embolism. Bosn J Basic Med Sci. 2020;20(2):248–53.
26. Salinger-Martinovic S, Dimitrijevic Z, Stanojevic D, Momčilović S, Kostic T, Koracevic G, et al. Renal dysfunction as intrahospital prognostic indicator in acute pulmonary embolism. Int J Cardiol. 2020;302:143–9.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Visceral Toxocariasis Seropositivity and Possible Risk Factors in Patients with a Clinical Preliminary Diagnosis of Cystic Echinococcosis*

*Kistik Ekinokokkoz Klinik Ön Tanılı Hastalarda Visceral Toxocariasis Seropozitifliği ve Olası Risk Faktörlerinin Değerlendirilmesi**

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ABSTRACT

Aim: *This study aimed to evaluate the seropositivity and possible risk factors for visceral toxocariasis in patients with a clinical preliminary diagnosis of cystic echinococcosis.*

Material and Methods: *Between October 2022 and December 2023, 184 blood serum samples, which were taken from patients with a clinical preliminary diagnosis of cystic echinococcosis and sent to the Medical Parasitology Laboratory of the Health Research and Training Hospital of Kafkas University, were analyzed for anti-Toxocara canis IgG using ELISA. Anti-Ascaris lumbricoides IgG ELISA was applied to the positive samples to differentiate cross-reactions.*

Results: *In this study, anti-T.canis IgG positivity was detected in 73 (39.67%) of the 184 serum samples. Among the sera determined to be positive for anti-T.canis IgG, mixed infection with A.lumbricoides was detected in 38 (52.05%) samples, and cross-reactions were identified in 10 (13.7%) samples. The study revealed the overall positivity rate for anti-T.canis IgG alone as 23.97% (35/146), with rates of 24.47% (23/94) in women and 23.08% (12/52) in men. Out of the 6 samples positive for cystic echinococcosis (6/184; 3.26%), 3 (3/6; 50%) were also seropositive for visceral toxocariasis. Anti-T. canis IgG was detected at higher rates in women, individuals over 65 years of age, illiterates, farmers, and rural inhabitants (P >0.05). The levels of anti-T.canis IgG were significantly higher in individuals with detached houses with gardens, those who kept dogs in their gardens, those with vegetable patches, those with neighboring gardens and surroundings with dogs, and those engaged in soil-related garden work (P <0.05).*

Conclusions: *In Kars and its surroundings, visceral toxocariasis was significant for public health, especially among individuals in contact with stray dogs and in soil-related occupations. Further studies are needed to determine the correlation between visceral toxocariasis and cystic echinococcosis, which share similar epidemiologic risks and clinical complaints.*

Key words: *anti-Toxocara canis IgG; risk factor; visceral toxocariasis; cystic echinococcosis*

ÖZET

Amaç: *Bu çalışmada kistik ekinokokkoz klinik ön tanılı hastalarda visceral toxocariasis seropozitifliği ve olası risk faktörlerinin değerlendirilmesi amaçlandı.*

Gereç ve Yöntem: *Kafkas Üniversitesi Sağlık Araştırma ve Uygulama Hastanesi Tıbbi Parazitoloji laboratuvarına Ekim 2022-Aralık 2023 tarihlerinde kistik ekinokokkoz klinik ön tanılı hastalardan gönderilen 184 kan serum örneği anti-Toxocara canis IgG yönünden ELISA ile analiz edildi. Pozitif örneklere çapraz reaksiyonları ayırt etmek için anti-Ascaris lumbricoides IgG ELISA uygulandı.*

Bulgular: *Çalışmada, 184 serum örneğinin 73 (%39,67)'ünde anti-T.canis IgG pozitifliği saptandı. Anti-T.canis IgG saptanan örneklerden 38 (%52,05)'inde A.lumbricoides ile miks enfeksiyon, 10 (%13,7)'unda ise çapraz reaksiyon belirlendi. Araştırmada sadece anti-T.canis IgG pozitifliği %23,97 (35/146) bulunmuş olup, bu oran kadınlarda %24,47 (23/94) ve erkeklerde %23,08 (12/52) olarak belirlendi. Kistik ekinokokkoz pozitif bulunan altı (6/184; %3,26) örneğin üçünde (3/6; %50) visceral toxocariasis seropozitif saptandı. Anti-T.canis IgG; kadınlarda, 65 yaş üstü bireylerde, okur-yazar olmayanlarda, çiftçilerde ve kırsalda yaşayanlarda daha yüksek oranda tespit edildi (P >0,05). Müstakil bahçeli evi olanlarda, evinin bahçesinde köpek bulunanlarda, evinin bahçesinde bostan varlığı olanlarda, komşu bahçesi ve çevresinde köpek varlığı olanlarda ve toprakla irtibatlı bahçe işleri ile uğraşı olanlarda daha yüksek oranda bulunan anti-T.canis IgG pozitifliği istatistiksel olarak anlamlı bulundu (P <0,05).*

Sonuç: *Kars ve çevresinde visceral toxocariasisin özellikle sahipsiz köpek irtibatlı ve toprak temaslı işlerle uğraşanlarda halk sağlığı yönünden önemli olduğu belirlendi. Benzer epidemiyolojik riskler ve klinik şikâyetleri paylaşan visceral toxocariasis ve kistik ekinokokkoz arasındaki korelasyonunun saptanması için daha fazla çalışmaya ihtiyaç duyulmaktadır.*

Anahtar kelimeler: *anti-Toxocara canis IgG; risk faktör; visceral toxocariasis; kistik ekinokokkoz*

*Derived from the Master's thesis of the first author entitled "Evaluation of Visceral Toxocariasis Seropositivity and Risk Factors in Patients with Clinically Pre-Diagnosed of Cystic Echinococcosis".

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Introduction

Human toxocariasis, also known as visceral toxocariasis, is a zoonotic parasitic infection of global public health significance and is caused by the larvae of the roundworms *Toxocara canis* and *Toxocara cati*. Dogs serve as the primary source of infection for humans. Humans are described among the paratenic hosts of these ascarids. Toxocariasis is transmitted to humans via the accidental ingestion of embryonated eggs, which are shed in the feces of infected dogs and gain infectivity by larval development when nested in the soil. The encapsulated larvae hatch from the eggs in the small intestine and, after perforating the intestinal wall and entering the vascular system, are disseminated throughout the body in the bloodstream. Visceral larva migrans (VLM) is an important clinical form of infection caused by damage caused by migrating larvae to several visceral organs[1].

A global assessment demonstrated that Indonesia, Malaysia, and Papua New Guinea ranked first in *Toxocara* spp. prevalence with seropositivity rates higher than 60%. Nigeria, Gabon, Colombia, Romania and Vietnam followed next, with prevalence rates ranging from 41% to 60%. *Toxocara* seropositivity in Türkiye is similar to that in Russia, Australia and Canada, ranging between 6–15%[2]. Several studies have been conducted on the seroprevalence of human toxocariasis in Türkiye[3–6], and seropositivity has been reported as 32.3–48.4% in the Istanbul province[7] and 45.9% in the Elaziğ province[8].

In the Kars region, the prevalence of adult *T.canis* parasites has been detected as 50% in dogs[9] and 20% in foxes[10], yet no regional data is available on human toxocariasis. On the other hand, the prevalence of cystic echinococcosis (CE) in patients with a clinical preliminary diagnosis of CE has been determined to be 14.9% in the Kars region[11]. Given this finding, the design of the present study was based on the assumption that visceral toxocariasis and CE, two major parasitic zoonoses of canine origin, are associated with each other.

The present study was aimed at the serological investigation (by the enzyme-linked immunosorbent assay, ELISA) of visceral toxocariasis in patients who were admitted to the polyclinics of the Health Research and Training Hospital of Kafkas University located in the city center of Kars, with various complaints and were either preliminarily diagnosed with or suspected of having CE, as well as the determination of seropositivity for anti-*Toxocara canis* IgG, and the assessment of the risk factors involved in the epidemiology of human toxocariasis.

Material and Methods

Ethics statement

The study received ethical approval from the Kafkas University Non-Interventional Clinical Research Ethics Committee, with decision number "80576354-050-99/107."

Study material

This study was conducted at the Health Research and Training Hospital of Kafkas University, located in the city center of Kars. The investigation was designed as a prospective study on outpatients admitted to the hospital's various polyclinics with a clinical preliminary diagnosis or suspicion of CE and for whom a laboratory diagnosis of CE was requested from the Parasitology Laboratory.

The study material comprised the venous blood samples of 184 patients aged 9–90 years and serologically diagnosed with CE after being referred to the Medical Parasitology Laboratory between October 2022 and December 2023. The blood samples underwent centrifugation at 3000 rpm/min at the Medical Parasitology Laboratory of the Health Research and Training Hospital of Kafkas University for the extraction of sera. The extracted serum samples were transferred in 200–500 ml volumes into sterile microcentrifuge tubes, labelled, and stored at -20°C until being analyzed.

ELISA analysis

The blood serum samples were analyzed to determine the presence of anti-*T.canis* IgG was performed using the NovaLisa *Toxocara canis* IgG ELISA Kit (Novtocg0450, NovaTec Immundiagnostica GmbH, Germany) according to the manufacturer's instructions. The blood sera, which were determined to contain anti-*T.canis* IgG were further analyzed for the presence of anti-*A.lumbricoides* IgG antibodies using the NovaLisa *A.lumbricoides* IgG ELISA kit (Novascg0020, NovaTec Immundiagnostica GmbH, Germany) to differentiate possible cross-reactions arising from *A.lumbricoides* infection.

IHA analysis

The routine laboratory diagnosis of CE was also performed at the Medical Parasitology Laboratory of the Health Research and Training Hospital of Kafkas University by means of the indirect hemagglutination assay (IHA) (Siemens Cellognost Echinococ, antibody

titers of ≥1/128 were considered positive, and titers of 1/64 were considered suspect). The results were used for the comparative analysis with anti-*T.canis* IgG seropositivity.

Statistical Analysis

The statistical analysis of the study data was performed with the chi-square test of independence. The direction of correlation between the categorical variables, P <0.05, the strength of correlation (fi coefficient) and the odds ratio was determined. The study design was based on analyzing all blood serum samples of patients with a preliminary diagnosis of CE for anti-*T.canis* IgG antibodies within the set time period, no sample size was predetermined.

The study was conducted pursuant to the institutional permit granted by the hospital, the approval of the Ethics Board of Kafkas University, and the signed voluntary participation forms of the patients. A questionnaire was developed and administered to evaluate demographic data, socioeconomic characteristics and visceral toxocariasis risk factors. Patients, either for whom data records were not available in the hospital registration system or who refused to share information, were excluded from the study, such that the analyses were based on the number of answers (n) received for each question.

Results

In this study, 73 (39.67%) samples were determined to be positive for anti-*T.canis* IgG and no statistically significant correlation was determined between seropositivity and sex (P >0.05) (Table 1).

Out of the 73 samples which were determined to be positive for anti-*T.canis* IgG, 38 (52.05%) displayed mixed infection with *A.lumbricoides*, and 10 (13.7%) presented with cross-reactions between *A.lumbricoides*. In this study, the overall rate of seropositivity for anti-*T.canis* IgG alone was determined to be 23.97% (35/146) (Table 2).

In this study, anti-*T.canis* IgG seropositivity was found to be 4.3% (27/111) in the Kars province and 22.2% (2/9) in the Ardahan province. In the study, the "n" value varied with the answers given to the questionnaire items. The distribution of the anti-*T.canis* IgG-positive samples for the demographic characteristics of the patients is presented in Table 3.

It was ascertained that the risk of acquiring visceral toxocariasis was 0.28-fold higher in individuals living in detached houses with a garden, when compared to those living in an apartment/flat, 2.54-fold higher in people keeping dogs in the garden of their houses, when compared to those with no dog in the house garden, 2.41-fold higher in individuals known to be engaged in growing greens and have a vegetable patch as part of their house garden, when compared to those with no such vegetable patch and cultivation activity, 3.07-fold higher in individuals with dogs present in the neighboring garden(s) and surroundings, compared to those not exposed to such contact, and 2.9-fold higher in people engaged in soil-related garden work, compared to those with no such activity (Table 3).

The present study demonstrated that most patients were determined to be seropositive for anti-*T.canis* IgG suffers from associating hepatic and pulmonary

Table 1. *Anti-T. canis IgG ELISA results of the blood serum samples positive for CE*

Sex	Number of samples (%)	Positive (%)	Suspect (%)	Negative (%)	P- value
Female	117 (63.59)	45 (38.46)	6 (5.13)	66 (56.41)	> 0.05
Male	67 (36.41)	28 (41.79)	4 (5.97)	35 (52.24)	
Overall	184	73 (39.67)	10 (5.43)	101 (54.89)	

Table 2. *Exclusively seropositivity for anti-T.canis IgG after exclusion of co-infection with A.lumbricoides*

	Anti-T.canis IgG			
Sex	Number of samples (%)	Positive (%)	Suspect (%)	Negative (%)
Female	94 (64.38)	23 (24.47)	6 (6.38)	65 (69.14)
Male	52 (35.62)	12 (23.08)	4 (7.69)	36 (69.23)
Overall	146	35 (23.97)	10 (6.85)	101 (69.18)

Table 3. *Seropositivity of T.canis according to sociodemographic characteristics and possible risk factors*

	Anti-T.canis IgG positivity		
Characteristic	n	%	P value / Odds ratio
Sex (n: 146)			
Female (n= 94)	23	24.47	> 0.05
Male (n= 52)	12	23.08	
Age (n: 120)			
9-24 years (n= 7)	0	0	> 0.05
25-44 years (n= 42)	7	16.67	
45-64 years (n= 45)	12	26.67	
65 years and older (n= 26)	10	38.46	
Educational level (n: 120)			
Illiterate (n= 35)	12	34.29	> 0.05
Primary school - Secondary school (n= 55)	12	21.82	
High school (n= 19)	4	21.05	
University (n= 11)	1	9.09	
Occupation (n: 120)			
Housewife (n= 73)	20	27.4	> 0.05
Farmer (n= 21)	6	28.57	
Civil servant (n= 12)	2	16.67	
Student (n= 5)	0	0	
Other (n= 9)	1	11.11	
Residency (n: 120)			
Urban (district/city center) (n=63)	13	20.63	> 0.05
Rural (Village) (n= 57)	16	28.07	
Dwelling type (n: 120)			
Apartment/flat (n= 37)	4	10.81	< 0.05 / 0.28
Detached house with garden (n= 83)	25	30.12	
Presence of dog(s) as house pet(s) (n: 120)			
Yes (n= 0)	0	0	N/A
No (n= 120)	29	24.17	
Presence of dog(s) in house garden (n: 120)			
Yes (n= 42)	15	35.71	< 0.05 / 2.54
No (n= 78)	14	17.95	
Presence of vegetable patch as part of house garden (engagement in the growing of greens) (n: 120)			
Yes (n= 43)	15	34.88	< 0.05 / 2.41
No (n= 77)	14	18.18	
Presence of dog(s) in neighboring gardens and surroundings (n: 120)			
Yes (n= 86)	25	29.07	< 0.05 / 3.07
No (n= 34)	4	11.76	
Engagement in soil-related garden work (n: 120)			
Yes (n= 55)	19	34.55	< 0.05 / 2.9
No (n= 65)	10	15.38	

diseases, rheumatoid disease, gastroenteritis and allergic skin disorders. It was ascertained that 20 (22.99%) of the 87 patients were referred to the General Surgery Polyclinic, and 11 (22.45%) of the 49 patients were referred to the Internal Medicine Polyclinic. Overall, a large majority (88.6%, 31/35) of the 35 samples with visceral toxocariasis had been referred to by the General Surgery and Internal Medicine Polyclinics.

In this study, out of the 6 samples (6/184; 3.26%) determined to be seropositive for CE, 3 (3/6; 50%) were also ascertained to be seropositive for visceral toxocariasis.

Discussion

Human visceral toxocariasis is known to be more prevalent in tropical and subtropical regions, areas with limited control of the dog population, and low– and middle-income countries[1]. While the global prevalence of anti-*Toxocara* serum antibodies has been reported as 19%, regional prevalence has been detected to be highest in Africa (37.7%), lowest in the Eastern Mediterranean (8.2%), and to occur at levels of 34.1%, 24.2%, 22.8% and 10.5% in Southeastern Asia, the Western Pacific, America and Europe, respectively, with Nigeria, Romania, Argentina and Egypt displaying the highest country seroprevalences of 44%, 42%, 35% and 32%, respectively, and Japan, Spain and Italy the lowest detected seroprevalence of 4%[12]. The same researchers reported the prevalence in Türkiye as 7%. In a meta-analysis conducted by Ulloque-Badaracco et al.[13] for a period from 1990 to 2022, the general seroprevalence of human toxocariasis in Latin America and the Caribbean was determined as 31%, and seroprevalence was reported to be higher in dog owners.

Said et al.[14] reported the overall seroprevalence of anti-*T.canis* antibodies in different occupational groups in northwest Pakistan as 14.2% and demonstrated significant differences between the seropositivity rates of several subgroups about several variables such as income distribution, educational background and involvement in agricultural labor. Pezeshkian et al.[15] reported a toxocariasis seroprevalence of 5.8% in the adult population of the Kavar region of southern Iran. Luca et al.[16] reported a seropositivity rate of 22.64% in Romania and indicated that the elderly were affected more than children.

The seroprevalence of visceral toxocariasis has been reported as 5.14% in primary school children from China,[17] 7% in eosinophilic children from northwest Iran,[18] and 45.9% in the homeless and 27.8% in animal shelter workers from Brazil[19].

Previous researches from Türkiye has investigated the correlation of toxocariasis prevalence with several potential risk factors, including sex, age, socioeconomic status, occupation, pet animal ownership and geophagy[20]. To the authors' knowledge, there is no previous study on human *Toxocara* infections in the Kars region of Türkiye. On the other hand, seropositivity was reported as 48.4% in hypereosinophilic individuals from Istanbul in 2005[7] and 45.9% in schizophrenic patients from Elaziğ in 2008[8]. Anti-*T.can*is IgG seropositivity rates were reported as 12% in Bolu[6], 15% in Van[4], 16% in Isparta[21], 8% in farm workers from Muğla[22], 17.8% in chronic urticaria patients from Istanbul[23], 9.7% in asthma patients from Ankara[24] and 21.4% in different age groups from Kayseri[25]. Studies on the prevalence of visceral toxocariasis in children from Türkiye have reported rates of 7.6% in Kütahya[3], 12.95% in Izmir[26] and 32.3% in Sivas[27].

All of the patients enrolled in the present study were preliminarily diagnosed with CE and suffered from various clinical conditions and signs, including, among others, liver and lung diseases, gastrointestinal disorders and skin infections. The present study demonstrated a seropositivity rate of 23.97%, which is close to the global seroprevalence (19%) reported by Rostami et al.[12], and also falls within the seroprevalence range reported for European countries (4%–42%). However, no study has investigated the prevalence of *T.canis* in individuals with a prediagnosis of CE, and no head-to-head comparison has been made. On the other hand, the fact that our study was conducted in individuals with a prediagnosis of CE who had common epidemiologic risk factors and similar clinical symptoms made the group studied a special/selected group. Therefore, a higher seropositivity rate is expected to be detected than in other studies.

Despite having a high diagnostic accuracy (98.63% specificity and 96.92% sensitivity), the ELISA kit used in the present study was indicated by the manufacturer to produce cross-reactions for antibodies against *A.lumbricoides* and *Schistosoma*. In view of this possibility, the seropositive samples were subjected to a second analysis by ELISA, such that the serum samples were determined to be positive for anti-*T.canis* IgG was analyzed a second time by ELISA for anti-*A.lumbricoides* IgG antibodies. Due to *Schistosoma* infections not occurring in Türkiye, the anti-*T.canis* IgG-positive serum

samples were not analyzed for *Schistosoma* spp. As a result, 10 (10/73; 13.7%) of the anti-*T.canis* IgG-positive serum samples were suspected of being positive for anti-*A.lumbricoides* IgG antibodies, and these samples were assessed as having produced cross-reactions. On the other hand, we determined mixed infection with *T.canis* and *A.lumbricoides* in 38 (38/73, 52.05%) serum samples. This finding agrees with literature reports indicating individuals infected with *Toxocara* spp can be concurrently infected with the parasites *Toxoplasma gondii* and *Fasciola hepatica*[28,29].

As is the case with several other parasitic diseases, the epidemiology of visceral toxocariasis is affected by multiple risk factors. Although it is generally reported that visceral toxocariasis seropositivity is higher in women compared to men[12,30,31], the exact opposite has also been reported[15,19,32]. The present study did not show any statistically significant difference between men and women in the prevalence of visceral toxocariasis (P >0.05). While the occurrence of visceral toxocariasis has been reported to be high among children[25,33,34], due to increased exposure to parasite eggs with age, senile individuals have been reported to show a higher rate of seropositivity[14,16,19,35]. In agreement with these reports, in the present study, while anti-*T.canis* IgG positivity was not detected in the individuals aged 9–24 years, positivity was 16.67% in those aged 25–44 years, 26.67% in those aged 45–64 years, and 38.46% in those aged 65 years and older.

Higher visceral toxocariasis seropositivity rates have been reported in hunters, farmers and animal shelter workers[33], housewives[15], and rural inhabitants[17,36,37]. In agreement with these reports, the present study demonstrated an anti-*T.canis* IgG positivity rate of 28.07% in rural inhabitants and 20.63% in urban inhabitants (P >0.05).

Visceral toxocariasis seropositivity has been reported to be higher in dwellings of low quality and with poor hygiene conditions[38]. In the present study, anti-*T.canis* IgG positivity was determined to be 10.81% in those living in a flat and 30.12% in those living in a detached house with a garden (P <0.05, odds ratio, 0.28).

Multiple studies carried out in Türkiye and different regions of the world have pointed out significantly higher *Toxocara* positivity rates in individuals who either own dogs as pets, feed/take care of dogs inside or outside their houses, have close contact with dogs or share their living space with dogs[12,14,17,31,33,34]. In the present study, a statistically significant correlation was determined between anti-*T.canis* IgG positivity and the presence of dogs in the house garden, neighbouring garden or surroundings of the patients (P <0.05). The prevalence of visceral toxocariasis was 2.54-fold (odds ratio, 2.54) higher in patients keeping dogs in the garden of their house compared to those with no dog in their garden, and 3.07-fold higher (odds ratio, 3.07) in those with dogs in neighbouring gardens compared to those with no dog in neighbouring gardens. These findings show that the presence of dogs in the garden of the house of the patients or their neighbor's house significantly affected visceral toxocariasis seropositivity, and in agreement with the previous studies referred to above, demonstrated that these variables were not independent of each other.

Eggs shed in infected dogs' feces become infective within 3–4 weeks at a temperature range of 15–35°C. For this reason, soil-related garden work has been reported to increase visceral toxocarisis seropositivity[33,38,39]. Hence, in the present study, a higher rate of visceral toxocariasis was determined in patients involved in soil-related garden work and those with a vegetable patch as part of their house garden (P <0.05).

Seropositivity rates for visceral toxocariasis and CE, which usually share a common patient history of contact with dogs, similar epidemiological risks and common clinical complaints such as liver and lung diseases, were determined not to show any statistically significant correlation with each other in the present study. Nevertheless, 3 (50%) out of the 6 patients preliminarily diagnosed with CE had been determined to carry anti-*T.canis* IgG antibodies were considered to be an important finding. However, the low CE positivity rate (3.26%) made comparing and interpreting data difficult. Thus, there is a need for further studies on this particular issue.

Conclusion

A significantly high rate of visceral toxocariasis seropositivity was determined in the residents of Kars and its vicinity, and it was ascertained that several demographic and socioeconomic factors were involved in the epidemiology of this parasitic infection. It was concluded that the investigation of the correlation of visceral toxocariasis with CE should be based on a larger sample size and that further research is required from the one health perspective.

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Authors' Contribution

The authors share the responsibility for the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interests

The authors declare no potential conflicts of interest regarding this article.

Disclaimer

The content is solely the responsibility of the authors.

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References

1. Korkmaz M. Toxocariosis. In: Özcel MA. ed. Özcel'in Tıbbi Parazit Hastalıkları. İzmir: Türkiye Parazitoloji Derneği Yayını No:22. 2007. p. 649–660. (In Turkish) .
2. Ma G, Rostami A, Wang T, Hofmann A, Hotez PJ, Gasser RB. Global and regional seroprevalence estimates for human toxocariasis: A call for action. In: Bowman DD. ed. Advances in Parasitology. Toxocara and Toxocariasis, Volume 109, Elsevier Ltd. 2020. p. 275–290.
3. Akdemir C. Visceral larva migrans among children in Kutahya (Turkey) and an evaluation of playgrounds for T. canis eggs. Turk J Pediatr. 2010;52:158–62.
4. Çiçek M, Yılmaz H. Prevalence of Toxocariasis in human and dogs in Van Province. Kafkas Univ Vet Fak Derg. 2012;18:531–6.
5. Kustimur S, Dogruman Al F, Oguzulgen K, Bakir H, Maral I, Turktas H, et al. Toxocara seroprevalence in adults with bronchial asthma. Trans R Soc Trop Med Hyg. 2007;101:270–4.
6. Kutun S. Seroprevalance of Toxocariasis on people in Bolu and its region. Bolu Abant İzzet Baysal University, Health Sciences Intitute, Master Thesis, Bolu, Turkey, 2019.
7. Artinyan E, Uysal HK, Akgul O, Altiparmak S, Oner YA. Research on Toxocara canis antibodies obtained from patients with eosinophilia. Indian J Med Microbiol. 2014;32:383–6.
8. Kaplan M, Kalkan A, Kuk S, Demirdag K, Ozden M, Kilic SS. Toxocara seroprevalence in schizophrenic patients in Turkey. Yonsei Med J. 2008;49:224–9.
9. Umur Ş, Arslan MÖ. The prevalence of helminth species in stray dogs in Kars District. Türkiye Parazitol Derg. 1998;22:188–93.
10. Gıcık Y, Kara M, Sarı B, Kılıç K, Arslan MÖ. Intestinal parasites of Red foxes (Vulpes vulpes) and their zoonotic importance for humans in Kars province. Kafkas Univ Vet Fak Derg. 2009;15:135–40.
11. Arslan MÖ, Mor N, Bedir H. Seropozitifity of anti-Echinococcus granulosus in patients with clinical prediagnosis of Cystic Echinococcosis at Kafkas University Health Research and Application Hospital. Türkiye Parazitol Derg. 2022;46:129–32.
12. Rostami A, Riahi SM, Holland CV, Taghipour A, Khalili-Fomeshi M, Fakhri Y, et al. Seroprevalence estimates for toxocariasis in people worldwide: A systematic review and meta-analysis. PLoS Negl Trop Dis. 2019;13:e0007809.
13. Ulloque-Badaracco JR, Hernandez-Bustamante EA, Alarcón-Braga EA, Huayta-Cortez M, Carballo-Tello XL, Seminario-Amez RA, et al. Seroprevalence of human toxocariasis in Latin America and the Caribbean: A systematic review and meta-analysis. Front Public Health. 2023;11:1181230.
14. Said A, Khattak I, Abbas RZ, Khan MK, Saleemi MK, Budke CM, et al. Toxocara canis seropositivity in different exposure groups in the Khyber Pakhtunkhwa province of Northwest Pakistan. Parasitol Res. 2023;122:1159–66.
15. Pezeshkian F, Pouryousef A, Omidian M, Mikaeili F, Safarpour AR, Shojaei-Zarghani S, et al. Seroprevalence of toxocariasis and its associated risk factors among adult population in Kavar District, Fars Province, South of Iran: A cross-sectional community-based seroepidemiological survey. Interdiscip Perspect Infect Dis. 2023;2721202.
16. Luca I, Sîrbu CB, Sîrbu BJ, Cireşan A, Garedaghi Y, Dărăbuş G. A retrospective study on the seroprevalence of anti-T. canis antibodies in the human population of a Romanian City. Int J Med Parasitol Epidemiol Sci. 2022;3:24.
17. Wang S, Li H, Yao Z, Li P, Wang D, Zhang H, et al. Toxocara infection: Seroprevalence and associated risk factors among primary school children in central China. Parasite. 2020;27:30.
18. Pourgholaminejad A, Razipour H, Heydarian P, Ashrafi K, Roushan ZA, Sharifdini M. A Survey on the seroprevalence of toxocariasis and related risk factors in Eosinophilic Children of Northwest Iran. Afri Health Sci. 2022;22:617–25.
19. Santarem VA, do Couto AC, Lescano SZ, Roldán WH, Delai RR, Giuffrida R. Serosurvey of anti-Toxocara canis antibodies in people experiencing homelessness and shelter workers from São Paulo, Brazil. Parasit Vectors. 2022;15:373.
20. Taylan-Ozkan A. Sources and seroprevalence of toxocariasis in Turkey. Adv Parasitol. 2020;109:465–82.
21. Demirci M, Kaya S, Çetin ES, Arıdoğan B, Onal S, Korkmaz M. Seroepidemiological investigation of toxocariasis in the Isparta region of Turkey. Iranian Parasitol. 2010;5:52.
22. Sozen H, Citil BE, Caylak S, Gokmen AA, Kaya S, Demirci M, et al. Seroepidemiological study of toxocariasis among volunteers animal husbandry workers and veterinary in Southern Anatolia in Turkey in 2014. Iran J Parasitol. 2015;10:473.
23. Selek MB, Baylan O, Kutlu A, Özyurt M. Toxocara canis IgG seropositivity in patients with chronic urticaria. Iran J Allergy Asthma Immunol. 2015;14:450–6.
24. Kustimur S, Dogruman Al F, Oguzulgen K, Bakir H, Maral I, Turktas H. Toxocara seroprevalence in adults with bronchial asthma. Trans R Soc Trop Med Hyg. 2007;101:270–4.

25. Yazar S, Yaman O, Cetinkaya U, Hamamcı B, Şahin İ. Investigation of anti-Toxocara canis IgG antibodies in patients presenting at the Erciyes University Medical Faculty, Department of Parasitology. Türkiye Parazitol Derg. 2010;34:24–6.
26. Doğan N, Dinleyici EC, Bor O, Töz SO, Ozbel Y. Seroepidemiological survey for Toxocara canis infection in the northwestern part of Turkey. Türkiye Parasitol Derg. 2007;31:288–91.
27. Oğuztürk H, Saygı G. Investigation of infection caused by larvae of Toxocara canis in elementary school students. Türkiye Parasitol Derg. 2002;26:409–14.
28. Jones JL, Kruszon-Moran D, Won K, Wilson M, Schantz PM. Toxoplasma gondii and Toxocara spp. co-infection. Am J Trop Med Hyg. 2008;78:35–9.
29. Kim SW, Jang BK. Toxocara canis and Fasciola hepatica co-infection leading to hepatic abscess: A case report. J Korean Med Sci. 2023;38:e323.
30. Huang L, Sun L, Liu C, Li S, Zhang T, Luo X, et al. Diagnosis of ocular toxocariasis by serum and aqueous humor IgG ELISA. Transl Vis Sci Technol. 2021;10:33.
31. Zibaei M, Najmi M, Bahadory S, Miahipour A, Firoozeh F, Bakhshipour F. Sero-epidemiology of Toxocara canis infection in people attending four educational and therapeutic centres in Alborz Province, Iran. Med Srod. 2021;24:25–9.
32. Phuong NTN, Trung TT, Ha PH, Ha PTT, Anh LHN, Thao NTP, et al. Prevalence of Toxocara spp. infection: Investigate from the Thong Nhat Dong Nai General Hospital from 2019 to 2020. Am J Sci Eng Res. 2021;4:1.
33. Feckova M, Antolová D, Zaleśny G, Halánová M, Štrkolcová G, Goldová M, et al. Seroepidemiology of human toxocariasis in selected population groups in Slovakia: A cross-sectional study. J Infect Public Health. 2020;13:1107–11.
34. Mubarak AG, Mohammed ES, Elaadli H, Alzaylaee H, Hamad RS, Elkholy WA, et al. Prevalence and risk factors associated with Toxocara canis in dogs and humans in Egypt: A comparative approach. Vet Med Sci. 2023;29.
35. Na-Ek P, Narkkul U, Phasuk N, Punsawad C. Seroprevalence of anti-Toxocara canis antibodies and associated risk factors among dog owners in the rural community of Nakhon Si Thammarat province, southern Thailand. Trop Med Health. 2022;50:32.
36. Khoshsima-Shahraki M, Dabirzadeh M, Azizi H, Khedri J, Djahed B, Neshat AA. Seroepidemiology of Toxocara canis in children under 14 years referring to laboratories of Sistan and Baluchestan Province in Southeast of Iran. Iran J Parasitol. 2019;14:89–94.
37. Lee JY, Yang MH, Hwang JH, Kang M, Paeng JW, Yune S, et al. The prevalence of toxocariasis and diagnostic value of serologic tests in asymptomatic Korean adults. Allergy Asthma Immunol Res. 2015;7:467–75.
38. Bayoumy A, Atallah R, Mohamed K, Zaalouk TK, Ghazy MES, El-Kenany MA. Seroepidemiological evaluation of toxocariasis in Egyptian children suffering from recurrent urticaria. Egypt J Hosp Med. 2019;76:4262–8.
39. Etewa SE, Abdel-Rahman SA, Abd El-Aal NF, Fathy GM, El-Shafey MA, Ewis AM. Geohelminths distribution as affected by soil properties, physicochemical factors and climate in Sharkyia governorate. Egypt J Parasit Dis. 2016;40:496–504.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Comparing Predictive Accuracy of Bleeding in Total Abdominal Hysterectomy Among Anesthesiologists, Gynecologists and AI: A Clinical Observational Study

Total Abdominal Histerektomide Kanama Tahmini: Anesteziyologlar, Jinekologlar ve Yapay Zekâ Üzerine Klinik Gözlemsel Çalışma

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ABSTRACT

Aim: *Accurate prediction of perioperative blood loss is critical for optimizing outcomes in total abdominal hysterectomy (TAH). Traditional estimation methods by clinicians are subjective and prone to variability, while artificial intelligence (AI) offers a potential data-driven alternative. This study compares the predictive accuracy of anesthesiologists, gynecologists, and the AI algorithm ChatGPT4.0 for blood loss during TAH.*

Material and Methods: *This single-center, prospective observational study evaluated 50 patients who underwent TAH for benign conditions in 2023. Clinical data, including uterine size, surgical duration, and surgeon experience, were retrospectively collected. Participating gynecologists and anesthesiologists predicted intraoperative blood loss based on anonymized patient data. Predictions were compared to ChatGPT4.0's outputs and actual recorded blood loss, categorized into mild, moderate, and severe bleeding levels. Sensitivity, positive predictive value, and overall accuracy were analyzed using statistical tests appropriate for data distribution.*

Results: *Anesthesiologists achieved the highest overall accuracy (40%), excelling in moderate bleeding predictions. Gynecologists demonstrated moderate performance across all categories, with 38% accuracy. ChatGPT4.0 showed the lowest overall accuracy (34%) but outperformed clinicians in predicting severe bleeding (37.5% positive predictive value). Variability in clinician predictions highlighted the challenges of subjective estimation, while AI predictions demonstrated consistency but limited precision.*

Conclusions: *AI offers promise in enhancing objective blood loss prediction, particularly for severe cases. However, its performance remains inferior to clinician estimates in most scenarios, underscoring the need for further algorithm refinement and integration into clinical workflows. Future research should focus on long-term validation and addressing ethical challenges in AI adoption.*

Key words: *AI; anesthesiology; artificial intelligence; blood loss prediction; ChatGPT; gynecology; total abdominal hysterectomy*

ÖZET

Amaç: *Perioperatif kan kaybının doğru tahmini, total abdominal histerektomi (TAH) sonuçlarını optimize etmek için kritik öneme sahiptir. Klinik uzmanlar tarafından yapılan geleneksel tahmin yöntemleri öznel olup değişkenliğe yatkınken, yapay zekâ (YZ) veri odaklı bir alternatif sunma potansiyeline sahiptir. Bu çalışma, TAH sırasında anestezistlerin, jinekologların ve ChatGPT4.0 adlı YZ algoritmasının kan kaybı tahmin doğruluğunu karşılaştırmayı amaçlamaktadır.*

Gereç ve Yöntem: *Bu tek merkezli, prospektif gözlemsel çalışmada, 2023 yılında benign durumlar için TAH geçiren 50 hasta değerlendirildi. Uterus boyutu, cerrahi süresi ve cerrahın deneyimi gibi klinik veriler retrospektif olarak toplandı. Katılımcı jinekologlar ve anestezistler, anonimleştirilmiş hasta verilerine dayanarak intraoperatif kan kaybını tahmin etti. Tahminler, ChatGPT4.0'ın sonuçları ve gerçek kaydedilmiş kan kaybı ile karşılaştırılarak hafif, orta ve şiddetli kanama seviyelerine göre kategorize edildi. Verilerin dağılımına uygun istatistiksel testler kullanılarak duyarlılık, pozitif prediktif değer ve genel doğruluk analiz edildi.*

Bulgular: *Anestezistler, orta şiddetli kanama tahminlerinde üstünlük sağlayarak en yüksek genel doğruluğu (%40) elde etti. Jinekologlar tüm kategorilerde orta düzey performans sergileyerek %38 doğruluk sağladı. ChatGPT4.0, genel doğruluk açısından en düşük performansı (%34) gösterdi ancak şiddetli kanama tahminlerinde (%37.5 pozitif prediktif değer) klinisyenlerden daha iyi sonuç verdi. Klinisyen tahminlerindeki değişkenlik, öznel tahminin zorluklarını ortaya koyarken, YZ tahminleri tutarlılık sergilemiş ancak sınırlı bir kesinlik göstermiştir.*

Sonuç: *Yapay zekâ, özellikle şiddetli vakalar için objektif kan kaybı tahmini sağlamada vaat sunmaktadır. Bununla birlikte, mevcut performansı çoğu senaryoda klinisyen tahminlerinin gerisinde kalmakta olup, algoritmanın daha fazla iyileştirilmesi ve klinik iş akışlarına entegrasyonu gerekmektedir. Gelecek araştırmalar, uzun vadeli doğrulama ve YZ'nin benimsenmesindeki etik zorlukların ele alınmasına odaklanmalıdır.*

Anahtar Kelimeler: *yapay zekâ; anesteziyoloji; kan kaybı tahmini; ChatGPT; jinekoloji; total abdominal histerektomi*

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Introduction

Background

Hysterectomy is among the most frequently performed gynecologic surgeries worldwide, providing definitive treatment for a variety of benign and malignant uterine conditions. In the United States alone, hysterectomy remains the most common non-pregnancy-related major surgery for women, with over 600,000 procedures performed annually[1]. Despite its effectiveness in addressing uterine pathologies, TAH is associated with significant risks, including surgical site infections, vaginal cuff dehiscence, venous thromboembolism, injury to adjacent organs, and excessive bleeding[1,2]. Excessive intraoperative blood loss, defined as greater than 400 mL, is one of the most critical complications, with average estimated losses ranging from 300 to 400 mL and severe bleeding rates reported in up to 16.9% of cases across hospitals[2–4]. Surgery complicated by significant blood loss leads to adverse outcomes, including increased rates of transfusion, readmission, reoperation, prolonged hospital stay, and postoperative morbidity[4]. Patient and procedure-specific factors, such as uterine size, surgical duration, surgical route, and surgeon experience, contribute to variations in estimated blood loss, emphasizing the need for quality improvement initiatives[4–8]. Identifying factors and strategies that improve blood loss prediction and management remains vital for optimizing patient treatment and follow-up outcomes.

Accurate prediction of perioperative blood loss is a critical aspect of surgical planning and patient safety, influencing intraoperative strategies and postoperative outcomes. Traditional methods like visual estimation have inherent limitations, including significant interobserver variability and reliance on subjective judgment. These limitations are evident in studies comparing anesthesiologists and surgeons, where differences in observation angles and clinical focus result in inconsistent and often inaccurate blood loss estimates[9]. Recent advancements in artificial intelligence (AI), specifically machine learning (ML), have introduced innovative methods to predict surgical outcomes, including perioperative blood loss. A notable study applied a random forest algorithm to predict blood loss in orthognathic surgery and demonstrated a strong correlation between predicted and actual blood loss. The model achieved an average deviation of only 7.4 mL from actual values, with a standard deviation of 172.3 ml[10]. This highlights the potential of ML to address the limitations of traditional estimation methods, offering a more objective and data-driven approach to risk stratification and clinical decision-making. While ML-based predictions have been explored in orthognathic and other surgical fields, their application to gynecologic surgery, particularly TAH, remains underexplored.

Objectives

This study aimed to evaluate the accuracy of anesthesiologists' and gynecologists' blood loss estimates for the TAH procedure according to individual risk factors and physicians' personal experiences in our retrospective study cohorts by comparing them with the ML algorithm of ChatGPT4.0 with real-world data. By bridging the gap between traditional clinical observation and AI-driven prediction, this research seeks to enhance patient management in gynecologic surgery and provide a foundation for integrating AI tools into routine clinical practice.

Material and Methods

Study design

This prospective, single-center observational cohort study was conducted to evaluate the accuracy of blood loss predictions made by anesthesiologists, gynecologists and ChatGPT4.0 for patients undergoing TAH for benign indications. The study involved a retrospective cohort of 50 patients who underwent TAH at our hospital in 2023.

Ethics approval and consent to participate

The study was conducted after receiving approval from our tertiary referral hospitals' Clinical Investigations Ethics Committee on December 10, 2024 (Ethics number: KAEK-11/30.10.2024.221), by the principles of the Declaration of Helsinki. Due to the study's retrospective nature, no additional consent was obtained from the participants in the study cohort. However, all patients provided written informed consent upon admission for using their clinical records in scientific research, with a guarantee of anonymity, as approved by the local ethics committee. Participating physicians, including gynecologists and anesthesiologists, voluntarily provided their blood loss predictions after giving electronic consent. Predictions were based on anonymized clinical data without access to the actual intraoperative outcomes.

Setting

The study was carried out at our hospital's Gynecology and Obstetrics Department. Data collection of TAH was performed retrospectively using clinical records

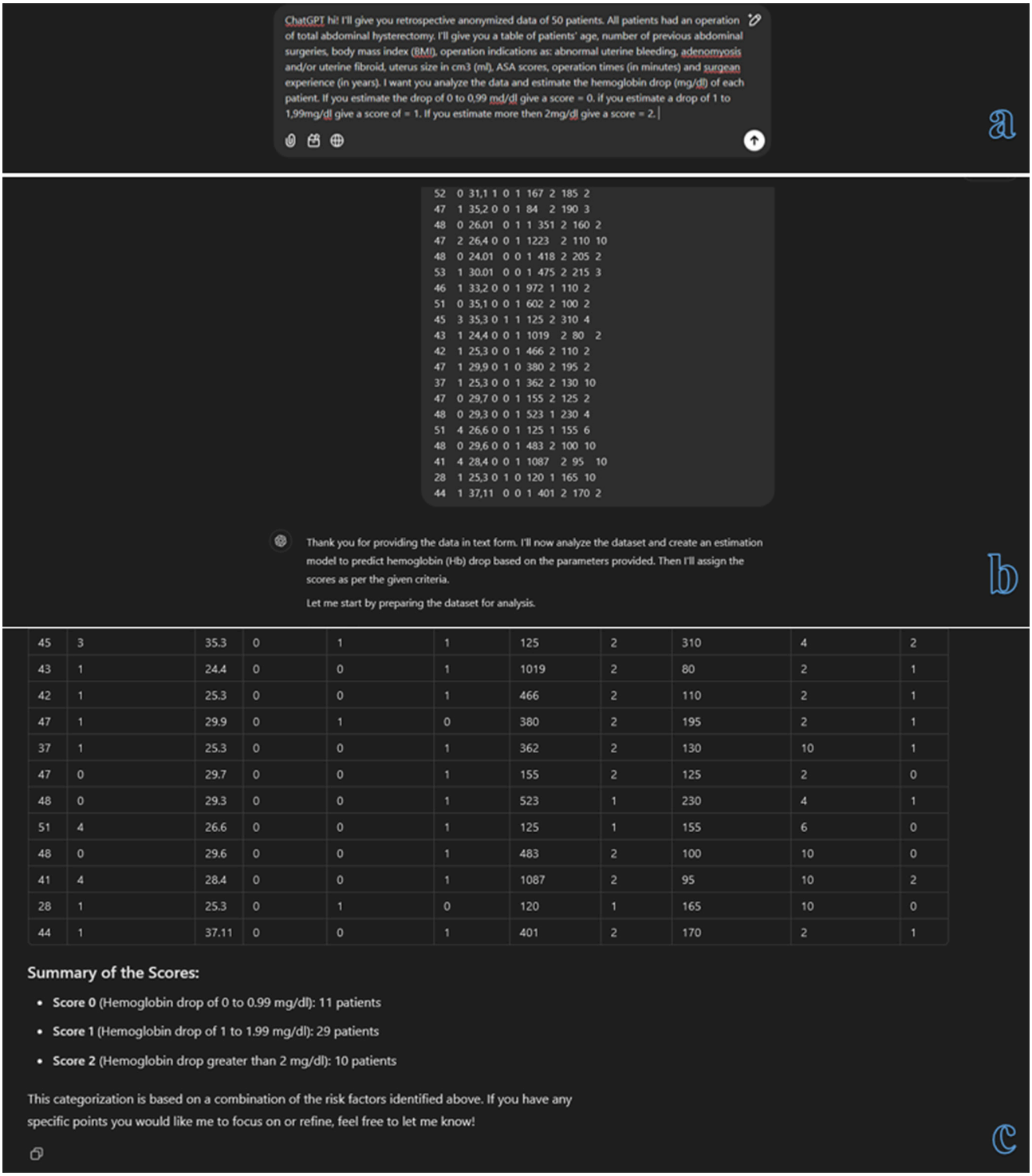

Figure 1. a–c. *Anonymized data of 50 patients was uploaded to ChatGPT4.0, and AI's predictions of blood loss for each case were recorded and analyzed. A detailed comment on ChatGPT4.0 is given for the process demanded (a). An anonymized input of 50 cases was uploaded (b). Output of AI was recorded and compared with the physician's results (c).*

from the first 50 operations performed in 2023. Predictions of intraoperative blood loss were obtained through anonymized electronic surveys distributed to participating physicians, ensuring that all data were de-identified. Also, anonymized data from 50 patients was uploaded to ChatGPT4.0, and AI was asked to predict the blood loss of each patient in the study cohort (Figure 1).

Participants

The study cohort included 50 patients who met the eligibility criteria: those who underwent TAH for benign indications in 2023, with complete clinical data available. These data included patient age, number of previous abdominal surgeries, body mass index (BMI), indications for surgery, preoperative and postoperative hemoglobin levels (mg/dl), uterine size obtained from imaging (cm^3), preoperative American Society of Anesthesiologists (ASA) score, total operative time (min) and the surgeon's years of experience are collected and analyzed. (Table S1, supporting information for full details) Patients undergoing TAH for malignant conditions were excluded from the study.

Variables

The primary outcome of interest was the accuracy of the blood loss predictions compared to the recorded intraoperative blood loss of retrospective real-world data. Predictor variables included patient age, BMI, operative indication, uterine size calculated from preoperative ultrasonographic imaging, ASA score, total operative time, and surgeon experience in years[4–8].

Data sources and measurement

Data were obtained from hospitals' digital archives and anonymized surveys. The accuracy of predictions was assessed by comparing the predicted blood loss from the physicians and ChatGPT4.0 with the recorded intraoperative blood loss documented in the patient's medical records.

Bias

Efforts were made to address potential biases by anonymizing participants and patient data and ensuring predictions were made without knowledge of actual outcomes. Reducing the study cohort to one year before the survey minimized recall bias.

Study size

The sample size was calculated using G*Power software, referencing prior research on predictive models for surgical outcomes[11,12]. With an alpha level of 0.05, an effect size of 0.495, and a statistical power of 95%, the required sample size was determined to be 46 patients. To improve reliability, 50 patients were included in the survey.

Quantitative variables

Uterine volume was calculated using the formula: Ultrasound length (cm)=2.94 + 0.75 × Pathology length (cm), highlighting the reliability of ultrasound as a predictive tool for pathological dimensions[13]. Blood loss was estimated in mL, and corresponding hemoglobin (Hb) decreases were categorized into three groups based on clinical thresholds and prior literature. Excessive intraoperative blood loss, defined as >400 mL, typically correlates with an approximate 1 mg/dL drop in Hb. This threshold was used to delineate the first category, 0–0.99 mg/dL, representing *mild or no significant blood loss*[4]. Further, studies suggest that blood losses exceeding 800–1000 mL are associated with a Hb drop of approximately ≥2 mg/dL. Thus, the second category, 1.00–1.99 mg/dL, was chosen to reflect *moderate blood loss*, and the third category, ≥2 mg/dL, captures cases of *severe blood loss*. This categorization was selected to align with practical clinical decision-making, particularly the thresholds for interventions such as autologous blood reinfusion or ordering bank blood[14]. By basing the Hb categories on these clinical correlations, the questionnaire allows for the stratification of blood loss severity and its impact on postoperative management, providing a standardized framework for analysis.

Statistical methods

The Shapiro-Wilk test was used to assess the data's distribution. A one-way ANOVA test was used for comparisons among three independent normally distributed groups, whereas the Kruskal-Wallis test was applied for non-normally distributed groups. Variables with a normal distribution are reported as mean ± standard deviation, while non-normally distributed data are presented as median (minimum-maximum). Categorical variables were compared using the chi-square test, with results expressed as numbers and percentages.

The performance of bleeding predictions was evaluated using a 3×3 confusion matrix, and positive predictive values, sensitivities (recall) and overall accuracies were calculated to assess prediction accuracy[15]. These metrics were computed for each bleeding severity category-mild, moderate, and severe-based on the median predictions made by gynecologists, anesthesiologists, and ChatGPT4.0.

All statistical analyses were conducted with IBM Statistical Package for Social Sciences (SPSS) program version 26.0, and a P-value of less than 0.05 was considered statistically significant.

Results

Participants

The demographic and clinical characteristics of the patient cohort (n=50) are presented in Table 1. The mean age of the patients was 46.14±5.52 years. Previous abdominal surgery had a median value of 1.0. The mean BMI was 29.36±4.07 kg/m². The mean uterine size was 625.70±620.41 mL, and the mean operation time was 141.80±52.36 minutes. Surgeon experience was reported as a median of 4.0 years. The surgical indications were distributed as follows: 10 (20.0%) patients underwent surgery due to abnormal uterine bleeding (AUK), 7 (14.0%) for adenomyosis, and 33 (66.0%) for fibroids. American Society of Anesthesiologists (ASA) scores were distributed as 24.0% (n=12) with a score of 1, 68.0% (n=34) with a score of 2, and 8.0% (n=4) with a score of 3. The mean preoperative hemoglobin level was 10.39±0.94 mg/dL.

Descriptive data

This study compared the bleeding prediction accuracy of gynecologists, anesthesiologists, and ChatGPT4.0 during total abdominal hysterectomy. Bleeding predictions were categorized into three levels: mild bleeding (0–0.99 mg/dL), moderate bleeding (1–1.99 mg/dL), and severe bleeding (≥2 mg/dL) (Table 2).

Table 1. *Analysis of retrospective study cohort demographic data of 50 elective total abdominal hysterectomy patients in 2023 according to their postoperative hemoglobin drop levels*

Demographic data		Mild or no significant blood loss (0–0.99 mg/dL) (n=18)	Moderate blood loss (1.00–1.99 mg/dL) (n=19)	Severe blood loss (≥2 mg/dL) (n=13)	P value
Age (years)		47.27±5.08	45.05±6.18	46.15±5.14	0.48
Pr. Abd. surgery (n)		0.00 (0.00–1.00)	1.00 (0.00–1.00)	1.00 (0.00–1.00)	0.11
BMI (kg/m²)		27.76±3.54	29.62±3.69	31.17±4.70	0.06
Uterine size (ml)		685.61±629.53	520.73±464.34	696.15±811.57	0.65
Op. time (min)		135.00±37.37	146.57±67.00	144.23±48.68	0.79
Surgeon exp. (years)		3.50 (2.00–10.00)	7.00 (1.00–10.00)	3.00 (1.00–9.00)	0.26
Indication	Ab. uterine bl.	2 (20%)	4 (40%)	4 (30.8%)	0.35
	Adenomyosis	3 (42.9%)	4 (57.1%)	0 (0.00%)	
	Ut. fibroid	13 (39.4%)	11 (33.3%)	9 (69.2%)	
ASA score	1	4 (33.3%)	4 (33.3%)	4 (33.3%)	0.27
	2	13 (38.2%)	13 (38.2%)	8 (23.5%)	0.64
	3	1 (25.0%)	2 (50.0%)	1 (25.0%)	0.42
Preop. Hb (mg/dl)		10.03±0.85	10.48±0.89	10.76±1.03	0.09

The Shapiro-Wilk test was used to assess the data's distribution. A one-way ANOVA test was used for comparisons among three independent normally distributed groups, whereas the Kruskal-Wallis test was applied for non-normally distributed groups. Variables with a normal distribution are reported as mean ± standard deviation, while non-normally distributed data are presented as median (minimum-maximum). Categorical variables were compared using the chi-square test, with results expressed as numbers and percentages.
Ab. uterine bl.: Abnormal uterine bleeding, ASA: American Society of Anesthesiologists, BMI: Body mass index, kg/m²: kilograms per square meter, mg/dl: milligrams per deciliter, min.: Minutes, ml: milliliters, n: Number, Op. time: Operation time, Pr. Abd. Surgery: Previous abdominal surgery, Preop. Hb: Preoperative hemoglobin, Surgeon exp: Surgeon experience, Ut. Fibroid: Uterine fibroid.

Table 2. *Comparison of anesthesiologist's, gynecologist's and ChatGPT4.0's bleeding predictions with 3×3 confusion matrix crosstabulation*

		Mild or no significant blood loss (0–0.99 mg/dL) (n=18)	Moderate blood loss (1.00–1.99 mg/dL) (n=19)	Severe blood loss (≥2 mg/dL) (n=13)	Positive predictive value	Overall accuracy
Gynecologist's predictions (median) (n=17)	Mild or no significant blood loss	5 (27.8%)	3 (15.8%)	4 (30.8%)	41.66%	38%
	Moderate blood loss	11 (61.1%)	11 (57.9%)	6 (46.2%)	39.28%	
	Severe blood loss	2 (11.1%)	5 (26.3%)	3 (23.1%)	30.00%	
Sensitivity (recall)		27.77%	57.89%	23.07%		
Anesthesiologist's predictions (median) (n=9)	Mild or no significant blood loss	2 (11.1%)	1 (5.3%)	1 (7.7%)	50.00%	40%
	Moderate blood loss	12 (66.7%)	16 (84.2%)	10 (76.0%)	42.10%	
	Severe blood loss	4 (22.2%)	2 (10.5%)	2 (15.4%)	25.00%	
Sensitivity (recall)		11.11%	84.21%	15.38%		
ChatGPT4.0's predictions	Mild or no significant blood loss	3 (16.7%)	5 (26.3%)	3 (23.1%)	27.27%	34%
	Moderate blood loss	13 (72.3%)	11 (57.9%)	7 (53.8%)	35.48%	
	Severe blood loss	2 (11.1%)	3 (15.8%)	3 (32.1%)	37.5%	
Sensitivity (recall)		16.66%	57.89%	23.07%		

The performance of bleeding predictions was evaluated using a 3×3 confusion matrix, positive predictive values.

Gynecologists (n=17) demonstrated 27.77%, 57.89%, and 23.07% sensitivity and 41.66%, 39.28%, and 30.00% positive predictive value for mild, moderate and severe bleeding, respectively, with a 38% overall accuracy. Anesthesiologists (n=9) performed 11.11%, 84.21%, and 15.38% sensitivity and 50.00%, 42.10%, and 25.00% positive predictive value for mild, moderate and severe bleeding, respectively, with an overall accuracy of 40%. ChatGPT4.0 demonstrated a lower overall accuracy of 34% compared to the other groups but performed better in predicting severe bleeding with a sensitivity of 23.07% and 37.5% positive predictive value. ChatGPT4.0 achieved a sensitivity of 16.66% and 23.07% for mild and moderate bleeding and a positive predictive value of 27.27% and 35.48%, respectively.

Discussion

Integrating artificial intelligence (AI) into clinical practice has shown significant promise but poses notable challenges that require careful consideration. Our study results reveal significant variability in the prediction accuracy, precision, and recall across the three groups and bleeding severity levels. While anesthesiologists demonstrated high precision in predicting moderate bleeding but had lower consistency in predicting mild and severe bleeding, gynecologists showed moderate performance across all bleeding categories. Still, they struggled with the precision and recall of severe bleeding predictions. ChatGPT4.0, while generally less precise and accurate than the other groups, achieved the highest accuracy in predicting severe bleeding.

One critical issue in clinical practice is the reliance on surgeons' subjective visual estimation, which can lead to significant underestimation or overestimation of blood loss, affecting clinical decision-making[16]. Similarly, a study cohort of laparoscopic surgeries has been found to carry risks of underestimating bleeding, emphasizing the need for more reliable quantitative methods[17]. Interestingly, AI's role as an assistive tool for clinicians presents a nuanced picture. Studies have shown that while AI systems such as GPT-4 outperform clinicians in isolated diagnostic tasks, their integration as diagnostic aids alongside clinicians has not consistently improved performance[18]. This highlights the need for further exploration into how clinicians can be effectively trained to work with AI systems and how these tools can be seamlessly integrated into workflows. For example, in laparoscopic colectomy, AI systems have shown proficiency in real-time detection of bleeding events, achieving remarkable precision[19]. Additionally, machine learning in predicting postpartum hemorrhage has proven effective, with random forest models yielding high accuracy in quantitative assessments[20].

Despite the advancements in medical technology, ethical and legal considerations remain a major barrier to the widespread adoption of AI in clinical practice. For instance, issues surrounding data privacy, potential biases in AI algorithms, and robust regulatory frameworks must be addressed to ensure equitable and responsible use[21]. Furthermore, the psychological and financial burdens stemming from AI's unexplained algorithm could hinder its acceptance among patients and clinicians alike, often referred to as the "black box" problem, raises ethical concerns regarding transparency, patient autonomy, and psychological trust[22].

Limitations

This study has several limitations that could influence its outcomes and interpretations. Firstly, relying on retrospective datasets for analysis introduces inherent biases, including selection bias and inaccuracies in historical records. While AI-assisted tools demonstrated promise in diagnostic accuracy, their'efficacy was evaluated in a controlled environment, which may not reflect real-world challenges. Additionally, the ethical implications of the "black box" nature of AI systems highlight a critical limitation: the difficulty in understanding and validating the reasoning behind AI-driven decisions, which could undermine clinician trust and patient autonomy. Lastly, like the other studies in the literature, this study lacked long-term validation of AI implementation outcomes. While promising short-term results were reported, the absence of long-term outcomes remains an underexplored paradigm of the nature of the ML algorithms.

Interpretation

The findings of this study underscore the transformative potential of AI in healthcare, particularly in enhancing diagnostic accuracy and supporting objective clinical decision-making. However, given the study's limitations, these results should be interpreted cautiously. While ChatGPT demonstrated significant

accuracy in hemorrhage prediction, real-time integration into routine practice requires careful consideration of context, data quality, and clinician training.

Generalizability

Despite the study's limitations, our findings provide valuable insights into ChatGPT's potential in healthcare. To enhance generalizability, future research should focus on long-term validating AI systems in varied clinical environments, incorporating diverse patient populations, and addressing disparities in data representation in different languages. By doing so, AI technologies' broader applicability and equity in healthcare can be more effectively realized.

Conclusion

In conclusion, while AI holds the potential to revolutionize healthcare by improving diagnostic accuracy, reducing errors, and optimizing workflows, its integration into clinical practice must be approached with caution. A balance must be struck between leveraging AI's capabilities and addressing its ethical, practical, and educational challenges. Future research should focus on establishing comprehensive ethical guidelines to ensure that AI is a reliable and transparent partner in patient care.

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Conflict of interest

The authors declare no conflict of interest.

Availability of data and materials

This published article and its supplementary information files include all data generated or analyzed during this study.

References

1. Clarke-Pearson DL, Geller EJ. Complications of hysterectomy. Obstetrics & Gynecology. 2013;121(3):654–673.
2. Meeks GR, Harris RL. Surgical approach to hysterectomy: abdominal, laparoscopy-assisted, or vaginal. Clinical obstetrics and Gynecology. 1997;40(4):886–894.
3. Maresh M, Metcalfe M, McPherson K, Overton C, Hall V, Hargreaves J, et al. The VALUE national hysterectomy study: description of the patients and their surgery. BJOG. An International Journal of Obstetrics & Gynaecology. 2002;109(3):302–312.
4. English EM, Bell S, Kamdar NS, Swenson CW, Wiese H, Morgan DM. Importance of estimated blood loss in resource utilization and complications of hysterectomy for benign indications. Obstetrics & Gynecology. 2019;133(4):650–657.
5. Bonilla DJ, Mains L, Whitaker R, Crawford B, Finan M, Magnus M. Uterine weight as a predictor of morbidity after a benign abdominal and total laparoscopic hysterectomy. The Journal of reproductive medicine. 2007;52(6):490–498.
6. Beck TL, Morse CB, Gray HJ, Goff BA, Urban RR, Liao JB. Route of hysterectomy and surgical outcomes from a statewide gynecologic oncology population: is there a role for vaginal hysterectomy? American Journal of Obstetrics and Gynecology. 2016;214(3):348. e1–348. e9.
7. Catanzarite T, Saha S, Pilecki MA, Kim JY, Milad MP. Longer operative time during benign laparoscopic and robotic hysterectomy is associated with increased 30-day perioperative complications. Journal of minimally invasive gynecology. 2015;22(6):1049–1058.
8. Vree FE, Cohen SL, Chavan N, Einarsson JI. The impact of surgeon volume on perioperative outcomes in hysterectomy. JSLS. Journal of the Society of Laparoendoscopic Surgeons. 2014;18(2):174.
9. Yüzkat N, Soyalp C, Gülhas N. Comparison of the Error Rates of an Anesthesiologist and Surgeon in Estimating Perioperative Blood Loss in Major Orthopedic Surgeries: Clinical Observational Study. Journal of Anesthesia/Anestezi Dergisi (JARSS). 2019;27(4)
10. Stehrer R, Hingsammer L, Staudigl C, Hunger S, Malek M, Jacob M, et al. Machine learning based prediction of perioperative blood loss in orthognathic surgery. Journal of Cranio-Maxillofacial Surgery. 2019/11/01/. 2019;47(11):1676–1681.
11. Kane S, Collins S, Sproat LA, Mangel J. Predictors of transfusion requirement among patients who undergo hysterectomy for benign disease. Journal of Gynecologic Surgery. 2012;28(2):113–115.
12. Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G* Power 3. 1: Tests for correlation and regression analyses. Behavior research methods. 2009;41(4):1149–1160.
13. Cantuaria GH, Angioli R, Frost L, Duncan R, Penalver MA. Comparison of bimanual examination with ultrasound examination before hysterectomy for uterine leiomyoma. Obstetrics & Gynecology. 1998;92(1):109–112.

14. Gunasekaran K, Punnagai K, Vijaybabu K. A comparative study of diluents (crystalloid vs colloid) in acute normovolaemic haemodilution (ANH). International Journal. 2014;5(2):64.
15. Landis J. The Measurement of Observer Agreement for Categorical Data. Biometrics. 1977;
16. Gluck O, Mizrachi Y, Kovo M, Divon M, Bar J, Weiner E. Major underestimation and overestimation of visual blood loss during cesarean deliveries: can they be predicted? Archives of Gynecology and Obstetrics. 2017;296:907–913.
17. Sato M, Koizumi M, Inaba K, Takahashi Y, Nagashima N, Ki H, et al. Gynecologists may underestimate the amount of blood loss during total laparoscopic hysterectomy. Obstetrics and Gynecology International. 2018;2018(1):3802532.
18. Goh E, Gallo R, Hom J, Strong E, Weng Y, Kerman H, et al. Large language model influence on diagnostic reasoning: a randomized clinical trial. JAMA Network Open. 2024;7(10):e2440969–e2440969.
19. Horita K, Hida K, Itatani Y, Fujita H, Hidaka Y, Yamamoto G, et al. Real-time detection of active bleeding in laparoscopic colectomy using artificial intelligence. Surgical Endoscopy. 2024;38(6):3461–3469.
20. Wang M, Yi G, Zhang Y, Li M, Zhang J. Quantitative prediction of postpartum hemorrhage in cesarean section on machine learning. BMC Medical Informatics and Decision Making. 2024;24(1):166.
21. Alowais SA, Alghamdi SS, Alsuhebany N, Alqahtani T, Alshaya AI, Almohareb SN, et al. Revolutionizing healthcare: the role of artificial intelligence in clinical practice. BMC medical education. 2023;23(1):689.
22. Xu H, Shuttleworth KMJ. Medical artificial intelligence and the black box problem: a view based on the ethical principle of "do no harm". Intelligent Medicine. 2024;4(1):52–57.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Investigating the Professional Tenure on Burnout Among Academicians: A Cross-Sectional Analysis

Akademisyenlerde Mesleki Görev Süresinin Tükenmişlik Üzerindeki Etkisinin İncelenmesi: Kesitsel Bir Analiz

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ABSTRACT

Aim: *Burnout is a psychological condition resulting from prolonged exposure to workplace stress. This study investigates the relationship between burnout status and the years of professional experience among academic staff working at Pamukkale University.*

Material and Methods: *This single-center retrospective study included and investigated academic staff working at Pamukkale University between 2016 and 2017. Participants were divided into 1–9 years (Group 1, n=119) and 10+ years of professional tenure (Group 2, n=89). The demographic and work-related characteristics of the academic staff, including age, gender, weekly course load, and daily standing and seated work requirements, were recorded. Maslach Burnout Inventory (MBI) was utilized to evaluate burnout levels, and the Perceived Stress Scale was used to assess academic staff's perceived stress levels.*

Results: *The mean years of professional tenure in the academic staff were 3.73 in Group 1 and 18.74 in Group 2 (p=0.001). The mean age was 28.51 years in Group 1 and 43.55 years in Group 2 (p=0.001). When the groups' burnout state was analyzed, the emotional exhaustion and depersonalization domains of the MBI did not differ between groups (p>0.05). However, the personal accomplishment domain was significantly higher in Group 1 (p=0.001). An increase in Perceived Stress Scale score (β=0.569, p=0.001) and male gender (β=0.179, p=0.020) had an increasing effect, whereas an increase in daily sitting work time (β=-0.193, p=0.001) had a decreasing impact on MBI total score.*

Conclusions: *Reducing workloads can significantly increase the sense of personal accomplishment, especially over ten years of professional tenure. Academic staff with 1–9 years of tenure could benefit from supportive initiatives designed to avoid the complexities of academic promotion. Implementing mentoring programs may improve coping mechanisms, especially among male academic staff, who report being more vulnerable to burnout.*

Key words: *professional burnout; universities; workload; gender*

ÖZET

Amaç: *Tükenmişlik, işyeri stresine uzun süre maruz kalmaktan kaynaklanan psikolojik bir durumdur. Bu çalışmanın amacı, Pamukkale Üniversitesi'ndeki akademik personelin mesleki deneyim yıllarına göre tükenmişlik durumları arasındaki ilişkiyi araştırmaktır.*

Gereç ve Yöntem: *Bu tek merkezli retrospektif çalışmaya 2016–2017 yılları arasında Pamukkale Üniversitesinde çalışan akademik personel dâhil edildi ve incelendi. Katılımcılar 1–9 yıl (Grup 1, n=119) ve 10+ yıl (Grup 2, n=89) mesleki görev sürelerine göre ayrıldı. Akademik personelin yaş, cinsiyet, ortalama mesleki görev süresi, haftalık ders yükü ve günlük ayakta ve oturarak çalışma gereklilikleri gibi demografik ve işle ilgili özellikleri kaydedildi. Akademik personelin tükenmişlik düzeylerini değerlendirmek için Maslach Tükenmişlik Envanteri (MBI) ve algılanan stres düzeylerini değerlendirmek için Algılanan Stres Ölçeği kullanıldı.*

Bulgular: *Akademik personelin ortalama mesleki görev yılı Grup 1'de 3,73 ve Grup 2'de 18,74'tü (p=0,001). Yaş ortalaması Grup 1'de 28,51 yıl, Grup 2'de 43,55 yıldı (p=0,001). Grupların tükenmişlik durumları incelendiğinde, MBI'nın duygusal tükenme ve duyarsızlaşma alanları gruplar arasında farklılık saptanmadı (p>0,05). Ancak, kişisel başarı alt başlığı Grup 1'de anlamlı şekilde daha yüksekti (p=0,001). Algılanan Stres Ölçeği puanı artışı (β=0,569, p=0,001) ve cinsiyetin erkek olması (β=0,179, p=0,020) artırıcı; günlük oturarak çalışma süresi artışı (β=-0,193, p=0,001) ise MBI toplam puanı üzerinde azaltıcı etkiye sahipti.*

Sonuç: *İş yükünün azaltılması, özellikle on yıldan fazla görev süresi olanlarda kişisel başarı hissini önemli ölçüde artırabilir. Görev süresi 1–9 yıl arasında olan akademik personel, akademik terfinin karmaşıklığını önlemek için tasarlanan destekleyici girişimlerden faydalanabilir. Mentorluk programlarının uygulanması, özellikle tükenmişliğe karşı daha hassas olduklarını bildiren erkek akademik personel arasında başa çıkma mekanizmalarını geliştirebilir.*

Anahtar kelimeler: *mesleki tükenmişlik; üniversiteler; iş yükü; cinsiyet*

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Introduction

Burnout, a term used to describe a type of stress response or tension, is defined as a syndrome of emotional exhaustion and cynicism about one's work in response to chronic organizational stressors[1]. According to Maslach, burnout syndrome involves a complex process of emotional exhaustion, depersonalization, and loss of personal accomplishment[2]. As burnout progresses, individuals may perceive inadequacy in performing their job responsibilities and delivering services effectively[3]. The implications of burnout syndrome can be profound, displaying attendance issues and decreased job satisfaction, ultimately leading to a decline in work-related performance[4].

Academic professionals encounter numerous career challenges, particularly in teaching, supervision, and counseling. Pursuing scientific research and the imperative to publish can further exacerbate the pressures associated with academic workloads[5]. Demirbatir and Ergür[6] assert that the levels of burnout and stress within the academic community significantly impact the quality of education, contributions to the academic discipline, and innovative capacity. A study by Watts and Robertson[7] highlighted that burnout and job-related stress levels among university academicians are comparable to those experienced by healthcare personnel. Furthermore, Holmes et al.[8] identified that the prevalence of burnout syndrome among university academics ranges between 9 and 23.8%.

Burnout is not exclusive to the latter stages of one's career; it can emerge throughout an individual's professional trajectory[9]. Work overload can potentially deplete an individual's emotional resources, leading to physical and mental exhaustion and a decline in professional efficacy[8]. Prior research has indicated that social, demographic, and work-related variables may significantly influence the experiences of academics, revealing that younger, single, and childless individuals may encounter higher levels of occupational burnout compared to their married, older, or more experienced counterparts[10,11]. While age and tenure in the profession have not been identified as significant predictors of burnout[12], a discernible relationship exists between individual characteristics, such as age and marital status, and emotional burnout[13]. The emergence of burnout syndrome may be exacerbated by increased professional tenure; therefore, further investigation is warranted to elucidate the correlation between academic workload and burnout[7]. This study investigates the relationship between burnout status and years of professional experience among academic staff at Pamukkale University.

Material and Methods

Study Design

This single-center retrospective study included academic staff working at Pamukkale University between 2016 and 2017, whose evaluation forms were fully completed. Muş Alparslan University Scientific Research and Publication Ethics Committee confirmed the study's ethical approval (163406–2024/10/46). Informed consent was obtained from all academic staff included in the study. The study was carried out under the principles of the Declaration of Helsinki.

Study Sample

The inclusion criteria within the study's scope were as follows: a minimum of 6 months of employment at Pamukkale University, the ability to speak and understand the Turkish language, and a voluntary decision to participate in the study. Exclusion criteria included non-local academic staff with temporary assignments from other universities, those who had left or retired from Pamukkale University, and foreign national academics. The study population consisted of 1490 academic staff at Pamukkale University who met these criteria. Within the scope of the study, 1490 academic staff members from the different faculties were informed, and the academic staff who volunteered to participate filled out the questionnaires. 221 academic staff working at Pamukkale University participated and filled out the questionnaires. Two participants were excluded due to temporary assignments from other universities. The questionnaires of eleven participants were excluded because they were not filled out. Finally, the data of 208 academic staff whose evaluation forms were complete were analyzed. The participants were divided into two groups according to their professional tenure: Group 1 (0–9 years, n=119) and Group 2 (10+ years, n=89), as shown in the flow chart of the study (Figure 1).

Outcome Evaluations

The demographic characteristics of the academic staff, containing a range of variables such as mean years of professional experience, academic title, departmental affiliation, age, body mass index (BMI), gender, marital status, weekly course load, daily standing and seated

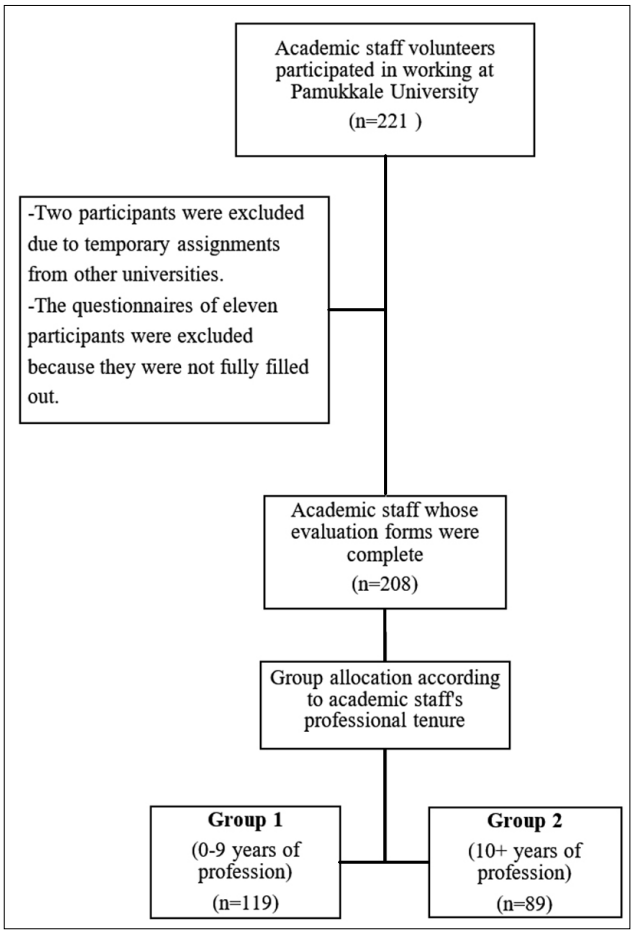

Figure 1. *Flow chart of the study.*

work requirements (in hours), and engagement in regular physical exercise were recorded. In addition, the study utilized the Maslach Burnout Inventory (MBI) to evaluate burnout levels and the Perceived Stress Scale to assess participants' perceived stress levels.

Maslach Burnout Inventory

The MBI is a 5-point Likert scale with 22 items: never, very rarely, sometimes, most of the time, and always. The MBI consists of three sub-dimensions. These are emotional exhaustion, depersonalization, and personal accomplishment. The emotional exhaustion subscale defines feeling exhausted and overwhelmed by one's job or work and consists of 8 items. The depersonalization subscale establishes the person's behavior towards those he/she serves in an emotionally deprived way, without considering that individuals are unique beings, and consists of 6 items. The personal achievement subscale defines feelings of competence and success in working with people and consists of 8 items. Burnout in the individual is characterized by high emotional exhaustion and depersonalization, with low-level personal accomplishment[14]. The group's burnout levels were defined as low, medium and high according to an earlier study design[15].

Perceived Stress Scale

The Perceived Stress Scale consists of 14 items and is designed to measure the extent to which certain situations in an individual's life are perceived as stressful. Participants rate each item on a 5-point Likert-type scale ranging from never (0) to very often (4). The 7 items with positive statements are reverse-scored. The lowest score that can be obtained from the Perceived Stress Scale is 0, and the highest score is 56[16].

Statistical Analysis

The IBM Statistical Package for Social Sciences (SPSS) version 27 (IBM, Armonk, NY, USA) program was used to analyze the data obtained statistically. Continuous variables are expressed as mean ± standard deviation, and categorical variables as numbers and percentages. The Kolmogorov-Smirnov test was used to test the normality of the variables analyzed. The Pearson Chi-square test was used to analyze categorical data. The Independent samples *t*-test was used to determine differences between groups for data fitting the normal distribution and the Mann-Whitney U test for data not fitting the normal distribution. Linear regression analysis was used to determine the factors influencing the burnout score of the academic staff. For all statistics, $p \leq 0.05$ was accepted as significant, and all results were expressed with 95% confidence intervals.

Results

The comparison of the groups' demographic data is presented in Table 1. The mean age was 28.51±3.10 years in the Group 1 and 43.55±7.26 years in the Group 2 (p=0.001). The BMI was 23.75±3.46 kg/m^2 in Group 1 and 25.68±4.26 kg/m^2 in Group 2 (p=0.001). Of the academic staff in Group 1, 47 (39.5%) were married, 70 (58.8%) were single, and 2 (1.7%) were divorced, whereas in Group 2, 75 (84.3%) were married, 8 (9%) single and 6 (6.7%) divorced (p=0.001).

Group 1 consisted of 4 lecturers (3.4%), 108 research assistants (90.8%), 6 doctor lecturers (5%), and 1 associate professor (0.8%). The academic staff's institutes were 35 (29.4%) in the School of Medicine, 21 (17.6%) were Faculty of Dentistry, 17 (14.3%) were Faculty of Physiotherapy and Rehabilitation, 14 (11.8%)

Table 1. *The demographic characteristics of the groups*

	Group 1 (n=119)	Group 2 (n=89)		
	Mean ± SD	Mean ± SD	t	p
Age (year)	28.51 ± 3.10	43.55 ± 7.26	t=-18.312	**0.001**
BMI (kg/m^2)	23.75 ± 3.46	25.68 ± 4.26	t=-3.598	**0.001**
	n (%)	**n (%)**	χ^2	
Gender				
Female	50 (42)	47 (52.8)	2.383	0.123
Male	69 (58)	42 (47.2)		
Marital status				
Married	47 (39.5)	75 (84.3)	54.515	**0.001**
Single	70 (58.8)	8 (9)		
Divorced	2 (1.7)	6 (6.7)		
Regular exercise				
Yes	58 (48.7)	61 (51.3)	1.413	0.235
No	36 (40.4)	53 (59.6)		
Smoking				
Yes	21 (17.6)	19 (21.3)	0.449	0.503
No	98 (82.4)	70 (78.7)		

SD: Standard deviation; BMI: Body mass index; kg: kilogram; m: meter
t: Student t-test

Table 2. *Work-related characteristics, burnout state, and the perceived stress level comparison of the groups*

		Group 1 (n=119)	Group 2 (n=89)		
		Mean ± SD	Mean ± SD	t/z	p
Years in profession		3.73 ± 2.31	18.74 ± 7.54	t=-18.140	**0.001**
Weekly course (hour)		1.71 ± 4.75	19.60 ± 10.46	z=-11.145	**0.001**
Daily seated working (hour)		6.12 ± 2.35	4.82 ± 2.11	t=4.127	**0.001**
Daily standing working (hour)		2.28 ± 1.86	3.78 ± 2.10	t=-5.423	**0.001**
Perceived stress scale		25.49 ± 7.30	24.61 ± 7.62	t=0.841	0.401
Maslach Burnout Inventory	Emotional exhaustion	10.39 ± 5.13	9.88 ± 6.32	t=0.623	0.534
	Depersonalization	7.46 ± 3.54	6.95 ± 3.07	t=1.078	0.282
	Personal accomplishment	12.31 ± 4.08	9.73 ± 3.46	t=4.818	**0.001**
	Total score	30.11 ± 8.78	26.57 ± 9.53	t=2.270	**0.006**
		n (%)	**n (%)**	χ^2	
Burnout state					
	Low	62 (52.1)	67 (75.3)		
	Medium	54 (45.4)	20 (22.5)	11.937	**0.003**
	High	3 (2.5)	2 (2.2)		

SD: Standard deviation
t: Student t-test; z: Mann-Whitney U test

were Engineering Faculty, 11 (9.2%) were Faculty of Economics and Administrative Sciences, 8 (6.7%) were Faculty of Education, 5 (4.2%) were Faculty of Science and Literature, 5 (4.2%) were Faculty of Divinity, 2 (1.7%) were Faculty of Sport Sciences, and 1 (0.8%) were Faculty of Health Sciences.

Group 2 consisted of 20 lecturers (22.5%), 8 research assistants (9%), 22 doctor lecturers (24.7%), 26 associate professors (29.2%), and 13 professors (14.6%). The academic staff's institutes were 19 (21.3%) in the School of Medicine, 15 (16.9%) were Faculty of Economics and Administrative Sciences, 13 (14.6%) were Faculty

of Science and Literature, 10 (11.27%) were Faculty of Sport Sciences, 8 (9%) were School of Foreign Languages, 7 (7.9%) were Faculty of Physiotherapy and Rehabilitation, 5 (5.6%) were Faculty of Education, 4 (4.5%) were Faculty of Dentistry, 3 (3.4%) were Faculty of Technology, 3 (3.4%) were Faculty of Health Sciences, and 2 (2.2%) were Faculty of Divinity.

The comparison of the groups' work-related characteristics, burnout state, and perceived stress level were presented in Table 2. The mean years of profession in the academic staff was 3.73±2.31 in Group 1 and 18.74±7.54 in Group 2 (p=0.001). The mean weekly course hours in the academic staff were 1.71±4.75 in Group 1 and 19.60±10.46 in Group 2 (p=0.001). Daily seated work in the academic staff was 6.12±2.35 in Group 1 and 4.82±2.11 in Group 2 (p=0.001). Daily standing working in the academic staff was 2.28±1.86 in the Group 1 and 3.78±2.10 in the Group 2 (p=0.001). Perceived stress scores did not differ between groups as the scores were 25.49±7.30 in the Group 1 and 24.61±7.62 in the Group 2 (p=0.401). When the groups' burnout state was analyzed, the emotional exhaustion subscale scores were 10.39±5.13 in Group 1 and 9.88±6.32 in Group 2 (p=0.534). The depersonalization subscale scores were 7.46±3.54 in the Group 1 and 6.95±3.07 in the Group 2 (p=0.282). Personal accomplishment subscale scores, however, were significantly higher in Group 1 as 12.31±4.08 and 9.73±3.46 in Group 2 (p=0.001). Total MBI scores were 30.11±8.78 in the Group 1 and 26.57±9.53 in the Group 2 (p=0.006). The group's burnout states of academic staff were 62 (52.1%) were low level, 54 (45.4%) were medium level, and 3 (2.5%) were high level of burnout in Group 1 whereas 67 (75.3%) were low level, 20 (22.5%) were medium level, and 2 (2.2%) were high level of burnout (p=0.003).

The linear regression analysis revealed that variables such as gender, mean years of profession, Perceived Stress Scale score, weekly course hours, daily standing and seated work status (in hours) were significantly effective in predicting the total score of the MBI (ΔR^2=41.8, p<0.001). In examining the influence of these variables on the MBI total score, it was determined that the Perceived Stress Scale score, gender (male), and daily seated work hours had significant effects (p<0.05). Conversely, the remaining variables did not show a significant impact (p>0.05). When comparing the magnitude of statistically significant variables related to the MBI total score, the following results were observed: Perceived Stress Scale score (β=0.569, p=0.001), daily seated work hours (β=-0.193, p=0.001), and gender (male) (β=0.179, p=0.020). The results of the linear regression analysis indicated that increases in Perceived Stress Scale score and male gender contributed positively to the total score of the MBI. However, the increase in the daily seated work hours had a decreasing effect.

Discussion

This investigation reveals that burnout levels, specifically in personal exhaustion and depersonalization, are comparable across both groups, with the 1–9 years of professional staff demonstrating a higher sense of personal accomplishment. Additionally, a medium level of burnout was more prevalent among academic staff with 10+ years of experience. In contrast, a low level of burnout was predominantly observed in the group with 1–9 years of experience. Interestingly, perceived stress scores did not differ significantly across the groups, suggesting a potential disconnect between objective workload and subjective stress experiences. The regression analysis identified three significant factors

Table 3. *Factors (variables) affecting Maslach Burnout Inventory total score*

	ΔR^2	F	ß	t	p value
	0.418	25.755			**<0.001**
Perceived stress scale score			0.569	10.583	**0.001**
Gender (male)			0.179	3.328	**0.001**
Weekly course hours			-0.107	-1.467	0.144
Mean years of profession			-0.126	-1.855	0.065
Daily standing work			-0.160	-1.843	0.067
Daily seated work			-0.193	-2.348	**0.020**

p value: Linear regression analysis results, ΔR^2: Additional variance rate, F: Model significance test, ß: Regression coefficient, t: t test statistics

affecting burnout: higher perceived stress scores and being male are linked to increased burnout, while increased daily seated work hours are associated with lower burnout levels.

Burnout is conceptualized as a psychological syndrome that arises from prolonged exposure to chronic interpersonal stressors within the workplace[17]. The implications of elevated burnout levels are significant, manifesting as lowered motivation, diminished job satisfaction, and an escalation in turnover rates, thereby contributing to a challenging organizational environment[18]. Prior research has identified several factors that influence burnout among academic staff, including the male gender, high-stress levels, physical job requirements, excessive workloads, inadequate job structure, and the lack of formal mentoring[19–23]. In a study conducted by El Mouedden et al.[1], the burnout levels among academic staff were assessed, revealing that 28.9% experienced low levels of burnout, 24.2% reported moderate levels, and a significant 46.9% indicated high levels of burnout. In this study, academic staff with 10+ years of profession exhibited higher weekly teaching hours and more daily standing work, while 1–9 years of academic staff reported greater daily seated work. However, both groups had similar male/female gender distributions and perceived stress levels. Our findings corroborate these previous studies, demonstrating that male gender, elevated stress levels, and increased work demands predict heightened burnout scores among academic staff. Furthermore, our analysis of academic staff with varying lengths of professional tenure revealed that those with 1–9 years of experience reported burnout levels of 52.1% at low, 45.4% at medium, and 2.5% at high levels. Conversely, those with 10 or more years of experience exhibited burnout levels of 75.3% at low, 22.5% at medium, and 2.2% at high levels. Our research indicates that male academic staff tend to experience higher levels of burnout than their female counterparts, likely due to workplace stressors and the physical demands of their roles.

Emotional exhaustion can stem from various sources, including prolonged stress, overwhelming responsibilities, and a lack of adequate support systems. Individuals experiencing emotional exhaustion often exhibit a noticeable decline in energy levels and may feel persistently fatigued[24]. This state of emotional depletion can lead to heightened sensitivity and an increased intolerance for social interactions, making it challenging to engage with others. As a result, they may withdraw from social situations, feeling overwhelmed by the demands of personal or professional relationships[25]. Recent research has indicated that burnout levels among academic staff tend to be relatively low to moderate across various university faculties[26,27]. These studies indicate that while academic roles are demanding, supportive colleagues, collaborative initiatives, and a sense of fulfillment help alleviate burnout among faculty members. Our results on the emotional exhaustion domain of the MBI demonstrated that groups have comparable scores, which suggests this outcome stems from similar workloads from environmental factors, coping mechanisms, and potential expectations of academic promotions. Those affected might find it difficult to concentrate or feel detached, exacerbating feelings of isolation and frustration. To cope with emotional exhaustion, it is essential to prioritize self-care, establish boundaries, and seek support, whether through professional help or by confiding in trusted friends and family. Recognizing the signs of emotional exhaustion and taking proactive steps can foster recovery and improve the overall well-being of the academic staff.

Depersonalization is a dimension of burnout that leads individuals to interact with others in a callous, detached, and emotionally hardened manner, resulting in negativity, irritability, and loss of idealism[28]. Those experiencing depersonalization may display negative or inappropriate behaviors, behaving unemotionally and carelessly toward people with interactions. This may lead to a vicious circle by affecting the perception of stress and burnout levels of the people interacting in the work environment[25]. Sağlam et al.[27] reported significant differences between academicians' depersonalization levels regarding their years of teaching experience. Kassim et al.[5] investigated academicians and found that the mean depersonalization score was 7.53 on the MBI. El Mouedden et al.[1] found that the mean depersonalization score was 9.87 on the professional burnout scale in academic staff, 28.9% were at a low level of burnout, 24.2% were moderate, and 46.9% indicated a high level of burnout. Our study findings of the academic staff on the depersonalization domain of the MBI was 7.46 in the 1–9 years group, whereas 6.95 in the 10+ years, without superiority to each other. Our finding showed lower scores in the depersonalization domain in both groups and suggests that the years of the profession may not be influencing the effect on the depersonalization domain. Other possible reasons for similar outcomes are the possible similar workload from environmental factors and coping mechanisms.

In addition, both samples include a wide range of disciplines, and the academic staff could develop coping mechanisms to struggle with burnout.

Previous research has highlighted the personal accomplishment domain of the MBI, reporting a mean score of 34.99, with 36.6% of participants exhibiting a high level of perceived lack of personal accomplishment[1]. Watts and Robertson[7] conducted a comprehensive analysis and determined that the normative value for educators and medical professionals in the personal accomplishment domain of the MBI was 33.54. Furthermore, an earlier study defined a low score in the personal accomplishment domain as equal to or less than 16, positing that higher scores correlate with an enhanced perception of personal accomplishment[1]. Additionally, research by Sağlam et al.[27] revealed an inverse relationship between years of teaching experience and personal accomplishment, whereby increased tenure correlated with diminished feelings of accomplishment. Our findings align with Sağlam et al.'s[27] findings, demonstrating that both cohorts under investigation exhibited significant deficiencies in personal accomplishment. Notably, academic staff with over 10 years of professional tenure reported lower personal accomplishment levels than their counterparts with 1 to 9 years of tenure. This finding suggests that new academic staff's ambitious desire for advancement may unexpectedly lead them to underestimate their achievement. This suggests that striving for promotion in the academic world may create pressure on individuals and negatively affect their subjective perception of success.

This study had several limitations. First, non-work-related stressors, chronic diseases, psychiatric history, and the socioeconomic status of the academic staff were not evaluated. Second, we did not assess potential problems with the institution or faculty management, possibly related to burnout syndrome. Lastly, the study could not assess physical activity levels, although this factor may affect physical and mental well-being.

Conclusion

This study elucidates that reducing course load and, consequently, heavy workloads can significantly enhance the sense of personal accomplishment among academic staff, particularly those with over ten years of professional tenure. In contrast, early-career academic staff may greatly benefit from structured supportive initiatives designed to assist them in navigating the complexities and pressures associated with academic promotion. Implementing mentorship programs and targeted professional development opportunities can improve coping mechanisms, especially among male academic staff, who have reported a heightened vulnerability to burnout. Future research should examine the longitudinal effects of workplace interventions on burnout, investigate discipline-specific stressors, and explore the role of organizational culture in triggering burnout.

References

1. El Mouedden I, Hellemans C, Anthierens S, Michels NR, DeSmet A. Experiences of academic and professional burnout in medical students and residents during first COVID-19 lockdown in Belgium: a mixed-method survey. BMC Med Educ. 2022;22(1):631.
2. Maslach C. The client role in staff burn-out. J Soc Issues. 1978;34(4):111–124.
3. Cordes CL, Dougherty TW. A review and an integration of research on job burnout. Acad Manage Rev. 1993;18(4):621–656.
4. Golembiewski RT, Boudreau RA, Sun BC, Luo H. Estimates of burnout in public agencies: worldwide, how many employees have which degrees of burnout, and with what consequences? Public Adm Rev. 1998;58(1):59–65.
5. Kassim MSA, Ismail R, Mohd Yusoff H, Ismail NH. How do academicians cope with occupational stressors to alleviate burnout? The experience of a research university. J Public Ment Health. 2020;19(1):35–45.
6. Demirbatır RE, Engür D. Academicians' Burnout, Vigor and Occupational Satisfactions in the Department of Fine Arts Education: A Sample of Uludag University. J Educ Train Stud. 2018;6(7):86–93.
7. Watts J, Robertson N. Burnout in university teaching staff: a systematic literature review. Educational Research. 2011;53(1):33–50.
8. Holmes ES, dos Santos SR, de Almeida AAF, Candeia RMS, Chaves LCMR, de Oliveira AEC, et al. Prevalence of burnout syndrome and factors associated with university teachers. Int Arch Med. 2017;10(49).
9. Boran T. Determination of burnout levels of teaching staff: Salihli Vocational School case study. ZKU Journal of Social Sciences. 2011;7(13):339–350.
10. Castelo-Branco C, Figueras F, Eixarch E, Quereda F, Cancelo M, Gonzalez S, et al. Stress symptoms and burnout in obstetric and gynaecology residents. BJOG. 2007;114(1):94–98.
11. Olkinuora M, Asp S, Juntunen J, Kauttu K, Strid L, Aärimaa M. Stress symptoms, burnout and suicidal thoughts in Finnish physicians. Soc Psychiatry Psychiatr Epidemiol. 1990;25(2):81–86.
12. Dikmetaş E, Top M, Ergin G. An examination of mobbing and burnout of residents. Turk Psikiyatri Derg. 2011;22(3):137–149.

13. Sherman AC, Edwards D, Simonton S, Mehta P. Caregiver stress and burnout in an oncology unit. Palliat Support Care. 2006;4(1):65–80.
14. Ergin C. Doktor ve hemsirelerde tukenmislik ve Maslach tukenmislik olceginin uyarlanması. VII. Ulusal Psikoloji Kongresi, 22th September 1992 Ankara (Türkiye). 1992.
15. Yuguero O, Forné C, Esquerda M, Pifarré J, Abadías MJ, Viñas J. Empathy and burnout of emergency professionals of a health region: A cross-sectional study. Medicine (Baltimore) . 2017;96(37):e8030.
16. Eskin M, Harlak H, Demirkıran F, Dereboy Ç. Algılanan stres ölçeğinin Türkçeye uyarlanması: güvenirlik ve geçerlik analizi. In New/Yeni Symposium Journal. 2013;51(3):132–140.
17. Singh C, Jackson D, Munro I, Cross W. Job experiences, challenges, revelations and narratives of nurse academics. A qualitative study. J Adv Nurs. 2022;78(8):2622–2633.
18. McPherson K, Barnard JG, Tenney M, Holliman BD, Morrison K, Kneeland P, et al. Burnout and the role of authentic leadership in academic medicine. BMC Health Serv Res. 2022;22(1):627.
19. Huda BZ, Rusli BN, Naing L, Winn T, Tengku MA, Rampal KG. Job strain and its associated factors among lecturers in the School of Medical Sciences, Universiti Sains Malaysia and Faculty of Medicine, Universiti Kebangsaan Malaysia. Asia Pac J Public Health. 2004;16(1):32–40.
20. Tsolakidis G, Vasiliki Diamantidou M. Nursing staff burnout: a critical review of the risk factors. Int J Caring Sci. 2022;15(1):668–679.
21. Akram Z, Sethi A, Khan AM, Zaidi FZ. Assessment of burnout and associated factors among medical educators. Pak J Med Sci. 2021;37(3):827–832.
22. Sánchez DV, García AJ, González Corzo I, Moreno MO. Psychosocial Factors and Burnout Syndrome in Academics of a Public University from Mexico. J Educ Psychol-Propositos y Representaciones. 2019;7(3):127–142.
23. Cañadas-De la Fuente GA, Ortega E, Ramirez-Baena L, De la Fuente-Solana EI, Vargas C, Gómez-Urquiza JL. Gender, Marital Status, and Children as Risk Factors for Burnout in Nurses: A Meta-Analytic Study. Int J Environ Res Public Health. 2018;15(10):2102.
24. Liu Y, Wang M, Chang CH, Shi J, Zhou L, Shao R. Work-family conflict, emotional exhaustion, and displaced aggression toward others: the moderating roles of workplace interpersonal conflict and perceived managerial family support. J Appl Psychol. 2015;100(3):793–808.
25. Akin U, Ulusoy T. The Relationship between Organizational Silence and Burnout among Academicians: A Research on Universities in Turkey. Int J High Educ. 2016;5(2):46–58.
26. Ardıç K, Polatcı S. Tükenmişlik sendromu akademisyenler üzerinde bir uygulama (GOÜ Örneği) . Gazi Üniversitesi İktisadi ve İdari Bilimler Fakültesi Dergisi. 2008;10(2):69–96.
27. Sağlam AS. Akademik Personelin sosyo-demografik özelliklerinin tükenmişlik düzeyleri ile ilişkisi/Relatıonshıp of socıo-demographıc characterıstıcs of academıcıans wıth theır burnout levels. Mustafa Kemal Üniversitesi Sosyal Bilimler Enstitüsü Dergisi. 2011;8(15):407–420.
27. Yoleri S, Bostancı MÖ. Determining the Factors that Affect Burnout and Job Satisfaction Among Academicians: A Sample Applicaton on the Hitit University. Electronic Turkish Studies. 2012;7(4):589–600.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Inflammatory Prognostic Index Predicts New-Onset Atrial Fibrillation in Patients After Primary Percutaneous Coronary Intervention in Patients with ST-Segment Elevation Myocardial Infarction

Enflamatuvar Prognostik Endeks, ST-Segment Yükselmeli Miyokard Enfarktüsü Olan Hastalarda Primer Perkütan Koroner Girişim Sonrası Yeni Başlangıçlı Atriyal Fibrilasyonu Öngörür

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ABSTRACT

Aim: *New-onset atrial fibrillation (NOAF) is an independent predictor of mortality and a strong indicator of poor prognosis following ST-segment elevation myocardial infarction (STEMI). The Inflammatory Prognostic Index (IPI) is clinically significant in predicting patient outcomes and serves as a novel inflammatory prognostic marker based on C-reactive protein (CRP), the neutrophil-to-lymphocyte ratio (NLR), and serum albumin levels. This study aimed to investigate the relationship between the IPI and NOAF in patients with STEMI who underwent primary percutaneous coronary intervention (pPCI).*

Material and Methods: *The population for this retrospective study consisted of 1.132 consecutive patients diagnosed with STEMI who underwent pPCI. Out of these, 946 patients were included in the study sample and were divided into two groups based on whether they developed NOAF or not.*

Results: *The study's primary outcome, that is, IPI was significantly higher in patients with NOAF than in those with No-AF (42.15 (17.6–81.7) vs. 12.77 (5.72–27.01), p<0.001) Univariate logistic regression analysis revealed significant correlations between NOAF; IPI, LVEF and age. Further analysis of these variables using the multivariate logistic regression analysis indicated that IPI (Odds Ratio [OR]: 2.026, 95% confidence interval [CI]: 1.081–3.799; p=0.028), LVEF and age were independent predictors for the development NOAF. Inflammatory prognostic index optimal cut-off value of >17.5 predicted NOAF with 76% sensitivity and 62.7% specificity (AUC: 0.740 [95% CI: 0.711–0.768, p<0.0001] (P <0.0001).*

Conclusions: *This study finds that the IPI independently predicts NOAF in STEMI patients treated with pPCI.*

Key words: *inflammatory prognostic index; ST-segment elevation myocardial infarction; atrial fibrillation*

ÖZET

Amaç: *Yeni başlangıçlı atriyal fibrilasyon (NOAF), ölümün bağımsız bir öngörücüsü ve ST-segment yükselmeli miyokard enfarktüsü (STEMI) sonrası kötü prognozun güçlü bir göstergesidir. Enflamatuvar Prognostik Endeks (IPI), hasta prognozunu tahmin etmede klinik öneme sahiptir ve C-reaktif protein (CRP), nötrofil-lenfosit oranı (NLR) ve serum albümin seviyelerine dayalı yeni bir enflamatuvar prognostik belirteç görevi görür. Bu çalışmanın amacı, STEMI geçiren ve primer perkütan koroner girişim (pPCI) geçiren hastalarda IPI ve NOAF arasındaki ilişkiyi araştırmaktır.*

Gereç ve Yöntem: *Bu retrospektif çalışmanın popülasyonu, pPCI geçiren STEMI tanısı almış 1132 ardışık hastadan oluşuyordu. Bunlardan 946 hasta çalışma örneğine dâhil edildi ve NOAF geliştirip geliştirmediklerine göre iki gruba ayrıldı.*

Bulgular: *Çalışmanın birincil çıktısı, yani IPI, NOAF'lı hastalarda AF'li olmayanlara kıyasla anlamlı derecede yüksekti (42,15(17,6–81,7) – 12,77 (5,72–27,01), p<0,001). Tek değişkenli lojistik regresyon analizi, NOAF, IPI, LVEF ve yaş arasında anlamlı korelasyonlar olduğunu ortaya koydu. Bu değişkenlerin çok değişkenli lojistik regresyon analizi kullanılarak daha ileri analizi, IPI'nin (Olasılık Oranı [OR]: 2,026, %95 güven aralığı [GA]: 1,081–3,799; p=0,028), LVEF'in ve yaşın NOAF gelişimi için bağımsız öngörücüler olduğunu gösterdi. IPI'nin >17,5'lik optimum kesme değeri, %76 duyarlılık ve %62,7 özgüllükle yeni başlangıçlı AF'yi öngördü (AUC: 0.740 [95% CI: 0,711–0,768, p<0,0001] (P <0,0001).*

Sonuç: *Bu çalışmanın bulguları, IPI'nin pPCI ile tedavi edilen STEMI hastalarında NOAF'ın bağımsız bir öngörücüsü olduğunu göstermektedir.*

Anahtar kelimeler: *enflamatuvar prognostik endeks, ST-segment yükselmeli miyokard enfarktüsü, atriyal fibrilasyon*

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Introduction

Research indicates that significant inflammation is a major factor in the onset of new atrial fibrillation (NOAF) among individuals experiencing acute ST-elevation myocardial infarction (STEMI)[1,2]. The occurrence of NOAF, a common outcome of acute STEMI, varies between 2.3% and 21%[3]. NOAF is a key predictor of mortality and strongly indicates a poor prognosis after STEMI[4,5]. Inflammation plays a significant role in developing and maintaining NOAF through myocyte necrosis, fibrosis, and infiltrating inflammatory markers[6]. Studies have shown that individuals with various subtypes of atrial fibrillation (AF) exhibit higher levels of certain inflammatory markers, including Interleukin-6 (IL-6) and High-Sensitivity C-Reactive Protein (Hs-CRP), compared to individuals in sinus rhythm[7].

A novel hematological biomarker that indicates a patient's inflammatory and immunological condition is the inflammatory prognostic index (IPI), which is calculated by combining the levels of CRP, neutrophil to lymphocyte ratio (NLR), and serum albumin (ALB) (IPI=CRP×NLR/ALB)[8]. Research has shown that this novel biomarker provides valuable insights into the prognosis of cancer patients, with elevated levels associated with worse outcomes. However, to our knowledge, no research has examined the impact of IPI on the likelihood of patients with STEMI developing NOAF. Therefore, we investigated the potential of IPI to predict NOAF in patients with STEMI who underwent primary percutaneous coronary intervention (pPCI).

Material and Methods

Population and Sample

This retrospective study included a population of 1.132 consecutive patients who were admitted to the emergency department of a tertiary heart center within 12 hours of the onset of symptoms and underwent pPCI between January 2019 and December 2023. Patients were excluded from the study if they were undergoing chemotherapy, had a history of concomitant inflammatory disorders, had received glucocorticoid therapy within the past three months, were pregnant or nursing, were in cardiogenic shock, had undergone cardiopulmonary resuscitation due to cardiopulmonary arrest, were receiving treatment with a thrombolytic agent, or were referred for emergency coronary artery bypass grafting. Additional exclusions included those with acute or chronic inflammatory diseases, neoplastic hematologic disorders, immunosuppressive medication use, major trauma or surgery within the last three months, missing blood cell count data, severe liver or kidney dysfunction, or those lost to follow-up. Ultimately, a total of 946 patients were included in the study sample. Among these patients, 892 did not present with AF, while 54 were identified as having NOAF. Patients were categorized into these two groups. Baseline demographic and clinical characteristics were gathered from the hospital's electronic database, and IPI was calculated for each patient. The study protocol received approval from the hospital's ethics and research committee and was conducted by the ethical principles outlined in the Declaration of Helsinki.

Laboratory Tests

The data included laboratory information such as neutrophil, lymphocyte, platelet, and hemoglobin counts, as well as biochemical parameters like serum albumin and C-reactive protein (CRP). The Inflammatory Prognostic Index (IPI) was calculated using the following formula: CRP × Neutrophil-Lymphocyte Ratio (NLR) / serum albumin[8].

Coronary Angiography and Percutaneous Coronary Intervention

All patients underwent coronary angiography via a femoral artery within 90 minutes of admission. They received 300 mg acetylsalicylic acid and a 180 mg oral loading dose of ticagrelor, 60 mg oral loading dose of prasugrel or 300 to 600 mg oral loading dose of clopidogrel, if not suitable for ticagrelor, on admission, as recommended in the recent European Society of Cardiology myocardial revascularization guidelines[9]. Standard intravenous bolus unfractionated heparin (70–100 U/kg) and additional doses were given to achieve an activated clotting time of >250 seconds before coronary intervention[9]. Stenting of the infarct-related artery with a drug-eluting stent was completed in suitable patients immediately after the coronary angiography.

Definitions

ST-segment elevation myocardial infarction (STEMI) was diagnosed based on the presence of typical chest pain lasting >30 min and/or other angina-equivalent symptoms, e.g., fainting, shortness of breath, dizziness, and sweating, with at least one of the following

electrocardiographic (ECG) findings, i. e., at least two contiguous leads with ST-segment elevation of ≥2.5 mm in men <40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women in leads V2-V3 and/or ≥1 mm in other leads [in the absence of left ventricular hypertrophy or left bundle branch block. In patients with inferior myocardial infarction (MI), right precordial leads (V3R and V4R) should be recorded for ST-segment elevation to determine concurrent right ventricular infarction. Similarly, ST-segment depression in leads V1-V3 signals myocardial ischemia, particularly when the terminal T-wave is positive (ST-segment elevation equivalent), and confirmation by simultaneous ST-segment elevation ≥0.5 mm in leads V7-V9 could be regarded as a way of identifying posterior acute myocardial infarction (AMI)[10].

To diagnose AF, ECG recordings obtained during hospital stays were analyzed. The evaluation focused on various parameters, such as irregular RR intervals, the presence of fibrillation waves, and the absence of P waves. Additionally, biochemical markers and morning venous blood samples collected during these hospital stays were reviewed afterward.

Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS, Statistical Product and Service Solutions for Windows) program version 22.0 (IBM Corp., Armonk, NY, U. S., 2013) software package was used for statistical analyses. The descriptive statistics obtained from the collected data were expressed as mean ± standard deviation in case of continuous variables determined to conform to the normal distribution, as median with 0.25 and 0.75 quantiles in case of continuous variables determined not to conform to the normal distribution, and as percentage values in the case of categorical variables. The t-test or Mann-Whitney U test was used to compare continuous variables between the groups, whereas Fisher's exact or chi-square test was used to compare categorical variables between the groups. Univariate Cox proportional hazards analyses were conducted for all clinically relevant variables that can potentially predict NOAF. Multivariate Cox regression analysis of variables found to be significant in univariate analyses, with stepwise backward conditional elimination, was performed to determine independent predictors of NOAF ($p < 0.05$). The significance level of selected variables was deemed 0.05 (a ¼ 0.05), and of the significant variables was deemed 0.10 (a ¼ 0.10). The IPI was analyzed using the multivariate Cox proportional hazards model as a continuous variable. The receiver operating characteristic (ROC) analysis was used to determine the optimal IPI score cut-off value for predicting NOAF.

Results

The baseline demographic, laboratory, and angiographic characteristics of the patients are presented in Table 1. The study included a sample of 946 patients with STEMI who underwent pPCI. The mean age of the participants was 56 years (±12 years), and 156 patients (16.6%) were female. Among the 946 patients, 892 were classified as No-AF patients, while 54 were categorized as having NOAF. There were no significant differences in mean systolic blood pressure (SBP), platelet count, creatinine levels, or the presence of an infarct-related left anterior descending coronary artery (LAD) between the No-AF and NOAF groups. However, patients with NOAF were older and had a higher proportion of females compared to those No-AF. The prevalence of hypertension (HT) and diabetes mellitus (DM) was significantly greater in the NOAF group, while smoking was more common among No-AF patients. The number of patients with a Killip class of 2 to 4 upon admission was also significantly higher in those with NOAF. Regarding laboratory findings, hemoglobin (Hgb), albumin, lymphocyte count, and left ventricular ejection fraction (LVEF) were all lower in NOAF patients. Conversely, white blood cell (WBC) counts, neutrophil counts and CRP levels were higher in this group. Additionally, heart rate, peak creatine kinase-myocardial band (CK-MB), glucose levels, time-to-treatment, and the SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score were significantly elevated in patients with NOAF (see Table 1).

In-Hospital Outcomes

The study's primary outcome, that is, IPI was significantly higher in patients with NOAF than in those with No-AF (42.15 (17.6–81.7) vs. 12.77 (5.72–27.01), $p<0.001$) (Table 1).

Independent Predictors of NOAF

Univariate logistic regression analysis revealed significant correlations between NOAF; IPI, LVEF and age (Table 2). Further analysis of these variables using the multivariate logistic regression analysis indicated that IPI (Odds Ratio [OR]: 2.026, 95% confidence interval [CI]: 1.081–3.799; p=0.028), LVEF (OR: 0.888, 95%

Table 1. *The baseline demographic, laboratory and angiographic characteristics of the patients with p-values*

	No AF (n: 892)		New-onset AF (n: 54)		All Patients (n: 946)		p-value
Age (years)	56	±12	64	±13	56	±12	**<0.001**
Patients with DM, n (%)	201	22.5	20	37	221	23.4	**0.015**
Gender, n (%) (Female)	142	15.9	15	27.8	157	16.6	**0.023**
Patients with HT, n (%)	351	39.3	35	64.8	386	40.8	**<0.001**
Active smokers, n (%)	518	58.1	20	37	538	56.9	**0.002**
Patients with Killip class >1 at admission, n (%)	123	13.8	23	42.6	146	15.4	**<0.001**
SBP (mmHg)	131	±31	131	±40	131	±31	0.734
Heart rate (bpm)	76	±16	87	±17	77	±16	**<0.001**
Hemoglobin level (g/L)	13.7	±1.74	12.8	±2.1	13.6	±1.77	**0.009**
WBC count (10^3/ml)	12.06	±3.6	13.6	±4	12.1	±3.6	**0.002**
Platelet count (10^3/ml)	259	±68	251	±71	258	±68	0.474
Neutrophil count (10^3/ml)	9.3	±3.4	11.01	±3.5	9.4	±3.4	**<0.001**
Lymphocyte count (10^3/ml)	0.17	(0.125-0.24)	0.135	(0.11-0.21)	0.170	(0.12-0.239)	**0.006**
Glucose level (mg/dL)	125	(103-163)	145	(112-210)	126	(104-168)	**0.025**
CRP (mg/dL)	9.6	(5.3-16.7)	16.6	(12–32.1)	9.9	(5.6-17.1)	**<0.001**
Albumin level (g/L)	36.89	±4.25	35.19	±5.76	36.79	±4.36	**0.018**
Creatine level (mg/dL)	0.92	±0.26	1.03	±0.39	0.93	±0.27	0.135
Peak CK-MB level (ng/Ml)	165	(98-298)	365	(210-443)	171	(100-311)	**<0.001**
LVEF (%)	47.7	±7.98	38.8	±8.2	46.7	±8.2	**<0.001**
Time-to-treatment (min.) or Total ischemic time	175	(110-265)	209	(128-325)	178	(112-267)	**0.001**
Patients with infarct-related LAD coronary artery , n (%)	453	50.8	34	63	487	51.5	0.082
SYNTAX score	16.6	±4.6	18.4	±3.8	16.7	±4.5	**<0.001**
IPI	12.77	(5.72-27.01)	42.15	(17.6-81.7)	13.29	(5.97-28.87)	**<0.001**

AF: atrial fibrillation, p: probability statistic, DM: diabetes mellitus, HT: hypertension, SBP: systolic blood pressure, bpm: beats per minute, WBC: white blood cell, CRP: C-reactive protein, CK-MB: creatine kinase-myocardial band, min: minute, LVEF: left ventricular ejection fraction, LAD: left anterior descending, SYNTAX: SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery, IPI: Inflammatory prognostic index.

Table 2. *Results of the univariate and multivariate analyses of the variables in terms of their prognostic value in predicting new-onset AF in patients with STEMI treated with pPCI*

	Univariate Analysis			Multivariate Analysis		
	Univariate OR, 95% CI		p-value	Multivariate OR, 95% CI		p-value
IPI	2.007	(1.038-4.011)	**<0.001**	2.026	(1.081-3.799)	**0.028**
LVEF	0.884	(0.853-0.916)	**<0.001**	0.888	(0.856-0.922)	**0.001**
Age	1.052	(1.029-1.076)	**<0.001**	1.034	(1.009-1.059)	**0.008**

AF: atrial fibrillation, STEMI: ST-segment elevation myocardial infarction, pPCI: primary percutaneous coronary intervention, OR: odds ratio, CI: confidence interval, p: probability statistic, LVEF: left ventricular ejection fraction, IPI: Inflammatory prognostic index.

CI: 0.856–0.922; p=0.001) and age (OR: 1.034, 95% CI: 1.009–1.059; p=0.008) were independent predictors for the development NOAF (Table 2).

Inflammatory prognostic index optimal cut-off value of >17.5 predicted new-onset AF with 76% sensitivity and 62.7% specificity (AUC: 0.740 [95% CI: 0.711–0.768, p<0.0001] (P <0.0001) (Figure 1).

Discussion

This study's findings indicate that the IPI is an independent predictor of NOAF in patients with STEMI treated with pPCI. To the best of the authors' knowledge, this is the first study to report the association between NOAF and IPI in patients with STEMI undergoing pPCI.

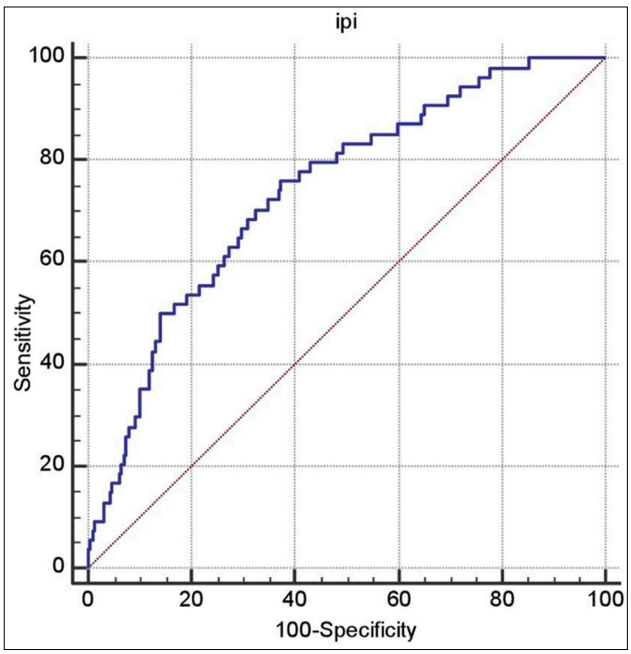

Figure 1. *ROC curve analysis of IPI index to predict new-onset atrial fibrillation in STEMI.*

Patients who receive thrombolysis or pPCI have a worse prognosis and higher death rates in the short, mid, and long term if they experience any additional AF events while hospitalized for acute STEMI[4,11]. The development of NOAF in individuals with STEMI has been linked to several clinical factors, consistent with earlier research[3,4]. We discovered that several factors are associated with an increased risk of NOAF in patients with STEMI. These factors include older age, reduced left ventricular ejection fraction (LVEF), and increased infarct size. The causes of NOAF are complex and involve several triggers. These include atrial ischemia, atrial dilation, increased sympathetic nervous system activity, and reduced vagal tone. Arrhythmic events can be initiated or worsened by acute hypoxia, hypokalemia, systemic and localized inflammation, and hormonal changes. Ultimately, this series of events leads to structural and electrical remodeling of the atria, resulting in AF[12]. After it develops, AF can lead to worsened ischemia, increased oxygen demand, and a higher heart rate. In addition to factors such as age, gender, obesity, smoking, diabetes mellitus, renal failure, chronic obstructive pulmonary disease, and history of arrhythmias, other clinical parameters that are recognized as risk factors for the onset of NOAF include elevated heart rate, increased size and volume of the left atrium, decreased LVEF, and HT[13]. In line with existing literature, our study found that the group that developed NOAF was older and had a higher prevalence of HT and DM. This group also exhibited higher heart rates and reduced LVEF. Notably, we found that smoking was more prevalent in the group without atrial fibrillation compared to the NOAF group.

The onset of new-onset atrial fibrillation (NOAF) and the rupture of atherosclerotic plaques, which can worsen STEMI, are significantly influenced by inflammation. Research has examined the ability of various inflammatory biomarkers to predict NOAF in patients with acute coronary syndrome (ACS). In individuals with STEMI, factors such as the neutrophil-to-lymphocyte ratio, systemic immune-inflammatory index, and prognostic nutritional index have been identified as independent predictors associated with NOAF[14–16]. Furthermore, while the CAR has not been documented in NOAF associated with STEMI, its relationship with postoperative atrial fibrillation following coronary artery bypass graft (CABG) has been reported[17].

The Inflammatory Prognostic Index (IPI) is a novel measure of inflammation that holds clinical significance for assessing prognosis. It is based on C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and serum albumin levels. Dirican et al. initially developed the IPI using hematological and biochemical markers to evaluate the prognosis of patients with non-small cell lung cancer[8]. Inflammatory prognostic index (IPI) is a simple, affordable, accessible, and noninvasive metric for predicting prognosis. Numerous studies on cancer patients have utilized it as a significant new measure to assess survival[8,18]. To our knowledge, no published research has examined the connection between IPI and NOAF. This study is the first to demonstrate a correlation between NOAF and IPI in STEMI patients undergoing pPCI.

Advanced age is recognized as an independent risk factor for AF[19]. Studies indicate elderly individuals are more likely to develop NOAF following a STEMI[20]. Our recent findings confirm that advanced age has significant prognostic value and is an independent risk factor for NOAF in STEMI patients undergoing initial pPCI. Furthermore, research by Asanin et al. demonstrated that patients who experienced AF after an acute myocardial infarction had a significantly lower LVEF compared to those who did not develop AF[21]. Our study also found that decreased LVEF is an independent risk factor for NOAF in the STEMI patient cohort.

Limitations of the Study

This study had several limitations. First, it was a single-center, retrospective study. Second, we only measured CRP, lymphocyte, neutrophil, and albumin levels at admission; we did not investigate how these levels changed over time or how those changes might have influenced the outcomes of patients with STEMI. Lastly, there is a need for comprehensive prospective studies to evaluate the impact of anti-CRP and other anti-inflammatory interventions in larger groups of STEMI patients, as the effectiveness of these treatments in improving outcomes for STEMI patients remains uncertain.

Conclusion

This study is the first to explore the association between the development of NOAF and the IPI in patients with STEMI who are treated with pPCI. To our knowledge, no prior research has investigated the relationship between IPI and NOAF. The increase in IPI may serve as an effective clinical indicator for assessing the risk of NOAF, exhibiting good sensitivity and specificity. The ability to predict the risk of NOAF in STEMI patients can be significantly enhanced by validating our findings through multicenter, prospective trials involving larger sample sizes.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Ethical Considerations

The study protocol was approved by the local ethics committee.

Informed Consent

Written informed consent was obtained from all patients.

Data Availability Statement

The authors confirm that the data supporting this study's findings are available within the article and that they have no additional data to share.

Contributorship

All authors contributed to the research's planning, conducting, and reporting. All contributors are responsible for the overall content.

References

1. Băghină RM, Crișan S, Luca S, Pătru O, Lazăr MA, Văcărescu C, et al. Association between inflammation and new-onset atrial fibrillation in acute coronary syndromes. J Clin Med. 2024;13:5088.
2. Tanık VO, Tunca Ç, Kalkan K, Kivrak A, Özlek B. The monocyte-to-HDL-cholesterol ratio predicts new-onset atrial fibrillation in patients with acute STEMI. Biomark Med. 2025;29:1–8.
3. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: A systematic review of the incidence, clinical features and prognostic implications. Eur Heart J 30:1038–45.
4. Wong CK, White HD, Wilcox RG, Criger DA, Califf RM, Topol EJ, et al. Significance of atrial fibrillation during acute myocardial infarction, and its current management: insights from the GUSTO-3 trial. Card Electrophysiol Rev. 2003;7:201–7.
5. Kinjo K, Sato H, Sato H, Ohnishi Y, Hishida E, Nakatani D, et al. Prognostic significance of atrial fibrillation/atrial flutter in patients with acute myocardial infarction treated with percutaneous coronary intervention. Am J Cardiol. 2003;92:1150–54.
6. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, et al. Inflammation as a risk factor for atrial fibrillation. Circulation. 2003;108:3006–10.
7. Ucar HI, Tok M, Atalar E, Dogan OF, Oc M, Farsak B, et al. Predictive significance of plasma levels of interleukin-6 and high-sensitivity C-reactive protein in atrial fibrillation after coronary artery bypass surgery. Heart Surg Forum. 2007;10:E131–5.
8. Dirican N, Dirican A, Anar C, Atalay S, Ozturk O, Bircan A, et al. A new inflammatory prognostic index, based on C-reactive protein, the neutrophil to lymphocyte ratio and serum albumin is useful for predicting prognosis in non-small cell lung cancer cases. Asian Pac J Cancer Prev. 2016;17:5101–6.
9. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al.;ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J Acute Cardiovasc Care. 2024;13:55–161.
10. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119–77.

11. Pizzetti F, Turazza FM, Franzosi MG, Barlera S, Ledda A, Maggioni AP, et al. GISSI-3 Investigators. Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: the GISSI-3data. Heart. 2001;86:527–32.
12. Ulus T, Isgandarov K, Yilmaz AS, Vasi I, Moghanchızadeh SH, Mutlu F. Predictors of new-onset atrial fibrillation in elderly patients with acute coronary syndrome under going percutaneous coronary intervention. Aging Clin Exp Res. 2018;30:1475–82.
13. Elliott AD, Middeldorp ME, Van Gelder IC, Albert CM, Sanders P. Epidemiology and modifiable risk factors for atrial fibrillation. Nat Rev Cardiol. 2023;20:404–17.
14. Wagdy S, Sobhy M, Loutfi M. Neutrophil/Lymphocyte ratio as a predictor of In-hospital major adverse cardiac events, new-onset atrial fibrillation, and No-reflow phenomenon in patients with ST elevation myocardial infarction. Clin Med Insights Cardiol. 2016;10:19–22.
15. Bağcı A, Aksoy F. Systemic immune-inflammation index predicts new-onset atrial fibrillation after ST elevation myocardial infarction. Biomark Med. 2021;15:731–39.
16. Hu X, Sang K, Chen C, Lian L, Wang K, Zhang Y, et al. Prognostic nutritional index and major cardiovascular events in patients undergoing invasive coronary angiography: a clinical retrospective study. J Pers Med. 2022;12:1679.
17. Aksoy F, Uysal D, Ibrişim E. Relationship between c-reactive protein/albumin ratio and new-onset atrial fibrillation after coronary artery bypass grafting. Rev Assoc Med Bras (1992). 2020;66:1070–76.
18. Erdoğan AP, Ekinci F, Karabaş A, Balçık OY, Barutça S, Dirican A. Could the inflammatory prognostic index predict the efficacy of regorafenib in patients with metastatic colorectal cancer? J Gastrointest Cancer. 2022;53:45–51.
19. He J, Yang Y, Zhang G, Lu XH. Clinical risk factors for new-onset atrial fibrillation in acute myocardial infarction: a systematic review and meta-analysis. Medicine (Baltimore) . 2019;98:e15960.
20. Wu N, Li J, Xu X, Yuan Z, Yang L, Chen Y, et al. Prediction Model of New Onset Atrial Fibrillation in Patients with Acute Coronary Syndrome. Int J Clin Pract. 2023;2023:3473603.
21. Asanin M, Perunicic J, Mrdovic I, Matic M, Vujisic-Tesic B, Arandjelovic A, et al. Prognostic significance of new atrial fibrillation and its relation to heart failure following acute myocardial infarction. Eur J Heart Fail. 2005;7:671–76.

EDİTÖRE MEKTUP / *LETTER TO THE EDITOR*

The Increasing Threat of Microplastics to Human Health

Mikroplastiklerin İnsan Sağlığına Yönelik Artan Tehdidi

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To the Editor,

I am writing to contribute an article addressing the emerging and critical issue of microplastics, which have become a pervasive environmental pollutant with significant implications for human health and disease. This article aims to highlight the effects of microplastics on human health and draw attention to the need for further research in this area. The increasing presence of microplastics in the environment is one of our time's most pressing, yet underrecognized, global health concerns. Microplastics are small plastic particles less than 5 millimeters in size. These microplastics, formed due to fragmentation, are pollutants in nature[1,2]. The spread of microplastics has reached an alarming level of potential health risks and necessitates research on their health effects.

Recent studies have shown that microplastics can be found naturally in aquatic ecosystems and enter the bodies of living organisms through various pathways, interacting with a number of physiological and chemical processes. Microplastics have been demonstrated in many tissues in the human body, including blood, lungs, and even placental tissues[1,3].

While the environmental consequences of microplastic contamination are well documented, their direct health effects on humans are still being investigated. Preliminary findings suggest that ingesting and inhaling microplastic particles may contribute to inflammation, oxidative stress, and impaired cellular function[4].

Primarily formed by the breakdown of larger plastic debris, microplastics can act as vectors for harmful pollutants such as persistent organic pollutants, heavy metals, and additives used in plastic production[5,6].

These toxins, often absorbed by microplastics, pose additional threats to human health by accumulating in tissues, disrupting endocrine functions, and contributing to chronic diseases such as cancer, respiratory disorders, and metabolic syndrome.

In light of these findings, it is critical to prioritize research investigating the full extent of microplastics' biological effects, particularly their interactions with the immune system, gastrointestinal system, and liver. While toxicological studies in laboratory animals have provided some data, establishing direct links to human health requires more rigorous epidemiological research.

Scientists should advocate for policies that regulate plastic production, improve waste management, and reduce plastic pollution. Interdisciplinary collaboration between different branches, such as environmental science, public health, and toxicology, is necessary to investigate the effects of microplastic exposure.

Long-term studies will be essential to determine the presence of microplastics in human tissues and their effects on the body.

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In conclusion, microplastics are a significant environmental and public health issue that requires further study. Long-term studies will show the extent to which microplastics play a role in the etiology of diseases. Medical and scientific communities must continue to investigate the effects on human health while advocating for regulations to reduce microplastic pollution. Translating research findings into policy is important to mitigate the adverse effects of microplastics. Initiatives aimed at reducing plastic production, improving waste management, and promoting biodegradable alternatives can significantly mitigate this global problem.

Thank you for considering this editorial contribution.

References

1. Zhao B, Rehati P, Yang Z, Cai Z, Guo C, Li Y. The Potential Toxicity of Microplastics on Human Health.pdf.
2. Zhu L, Kang Y, Ma M, Wu Z, Zhang L, Hu R, et al. Tissue Accumulation of Microplastics and Potential Health Risks in Human.pdf.
3. Vethaak AD, Legler J. Microplastics and human health.pdf.
4. Winiarska E, Jutel M, Zemelka-Wiacek M. The potential impact of nano- and microplastics on human health: Understanding human health risks. Vol. 251, Environmental Research. 2024.
5. Kadac-Czapska K, Knez E, Grembecka M. Food and human safety: the impact of microplastics. Crit Rev Food Sci Nutr [Internet]. 2024;64(11):3502–21.
6. Roslan NS, Lee YY, Ibrahim YS, Tuan Anuar S, Yusof KMKK, Lai LA, et al. Detection of microplastics in human tissues and organs: A scoping review. Vol. 14, Journal of Global Health. 2024. p. 04179.

Erratum: Comparison of Starion Vessel Sealing System with Conventional Technique and Harmonic Focus Ultrasonic Scalpel in Total Thyroidectomy

The incorrect word in titleinformation in the first page of the article with the title **"Comparison of Starion Vessel Sealing System with Conventional Technique and Harmonic Focus Ultrasonic Scalpel in Total Thyroidectom"** published in the **Kafkas J Med Sci 2024;14(3):217-223 (DOI: 10.5505/kjms.2024.71084),** word in the title has been corrected. The corrected and added part is as follows. We apologize to our readers.

Comparison of Starion Vessel Sealing System with Conventional Technique and Harmonic Focus Ultrasonic Scalpel in Total Thyroidectomy

Total Tiroidektomide Starion Damar Mühürleme Sisteminin Konvansiyonel Teknik ve Harmonik Odaklı Ultrasonik Cihaz ile Karşılaştırılması

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