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ORIGINAL ARTICLE

Competences and Attitudes of Internal Medicine Research Assistants Working in COVID-19 Inpatient Services About Nutrition: A Survey Study

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ABSTRACT

Objective: COVID-19 increases risk of malnutrition. With proper nutritional management, clinical outcomes are more positive but nutritional management is often overlooked. Aim of our study is to determine competences and attitudes of internal medicine research assistants working in COVID-19 services in terms of nutritional management and the factors that may affect this.

Materials and Methods: A 12-question survey was applied to internal medicine research assistants worked/still working in the inpatient service and intensive care units where COVID-19 patients were followed up. Their competences and attitudes about nutrition were learned.

Results: A hundred research assistants participated in the study. Ratio of those who considered their knowledge sufficient about nutrition management was 48% (n=48), enteral nutrition was 62% (n=62) and parenteral nutrition was 55% (n=55). There were 92 (92%) research assistants who thought that nutrition was a problem in COVID-19 patients, however there are only 6 (6%) research assistants who have read publications on nutritional management in COVID-19 patients. Research assistants who have performed intensive care or geriatrics rotation stated themselves more competent in nutrition ($p = 0.001$ & $p < 0.001$, respectively) and who have performed geriatrics rotation thought that they have sufficient knowledge about enteral nutrition ($p = 0.03$).

Conclusion: Research assistants who play important roles in the management of patients, find themselves highly incompetent in nutritional management, although they know that nutritional management will yield positive results on the patient's clinical outcomes. Importance of education of research assistants about nutrition should be emphasized in order to apply nutritional support better.

Keywords: nutritional assessment, malnutrition, COVID-19, education.

INTRODUCTION

The pandemic of COVID-19 poses unprecedented challenges and threats for patients and healthcare systems. Although the disease mainly affects the respiratory system [1], it can progress with multisystemic involvement [2]. Systemic diseases, inflammatory processes, immobility, hospitalization, intensive care unit stay increase the risk of malnutrition [3]. Malnutrition causes the prognosis of COVID-19 to be negative regardless of other factors. Complications are reduced and clinical results are observed to be better with proper nutritional management. Therefore, assessment and management of the nutritional status of COVID-19 patients is very important [4].

Physicians'knowledge about nutritional assessment may be incomplete and sometimes they may ignore this issue [5]. In the United States, nutrition education for physicians is insufficient in terms of scope, quality and duration due to various factors; this situation negatively reflects on clinical results [6]. It is stated that nutritional education is required in all medical faculties to overcome this insufficiency [7]. In addition, there are insufficiencies in nutrition education in fellowship training programs [8].

Although nutritional management has great importance in the pandemic of COVID-19 period, nutritional evaluation may often be underestimated. The aim of this study is to measure the competences and attitudes of internal medicine research assistants working in COVID-19 inpatient services about nutritional management.

MATERIALS AND METHODS

Study Design and Participants

Research assistants of Hacettepe University Faculty of Medicine Department of Internal Medicine who worked/were working in the inpatient services/ intensive care units where COVID-19 patients were hospitalized were included in the study. Research assistants who accepted to participate in the survey filled out a questionnaire containing twelve questions regarding the duration of their research assistantship, their rotations, how they see their competence and awareness about nutrition (Table 1). Questionnare is not a validiated questionnare and created by researchers.

Statistics

SPSS 24.0 (Armonk, NY: IBM Corp.) was used for statistical analysis. Descriptive statistics are used to describe the characteristics of research assistants. Pearson's chi-square and Fisher's exact tests was used to examine the relationship between the answers given to the survey questions and the characteristics of the research assistants. When p value is <0.05, it was considered statistically significant.

Ethical Approval

The study has acted in accordance with the Helsinki Declaration. Ethical approval was obtained from Non-interventional Clinical Researches Ethics Board of Hacettepe University Faculty of Medicine (#2021/02-29, 19.01.2021).

RESULTS

Descriptive Features

Survey questions were answered by 100 research assistants who agreed to participate in the study. Number of female participants was 52 (52%). Research assistants in the first 2 years was 36 (36%) and completed the first 2 years was 64 (64%). The ratios of participants who have performed geriatrics and intensive care rotation was 68% (n = 68) and 86% (n = 86) respectively. When the questions evaluating how they see their competencies about nutritional management are examined; 48 (48%) research assistants found themselves sufficient in nutritional management, 62 (62%) thought they had sufficient information about enteral nutrition indications and 55 (55%) thought they had sufficient knowledge about the indications for parenteral nutrition. Ratio of research assistants evaluating their hospitalized patients in terms of nutrition on a daily basis was 63% (n = 63). While 92 (92%) research assistants thought that nutrition was a problem in COVID-19 patients, 97 (97%) thought that nutritional treatments had a positive effect on clinical results, however, only 6 (6%) research assistants read publications on nutritional management in COVID-19 patients and 50 (50%) research assistants answered "sometimes" to the frequency of consultation to clinical nutrition unit in patients with malnutrition or malnutrition risk (Table 2).

Table 1. Survey

1. In what year of your assistantship are you?
…1 ….2 ….3 …..4 ….5
2. Have you worked in intensive care before?
…Yes …No
3. Have you done a geriatrics rotation?
…Yes …No
4. Do you find your knowledge about nutrition management competent?
…Yes …No
5. Could you evaluate each patient in terms of nutritional status in your daily clinical practice in inpatient wards?
…Yes …No
6. How often would you like a consultation to clinical nutrition unit for your patients with malnutrition or at risk of malnutrition?
…Always …Often …Sometimes …Never
7. Do you think you have enough information about enteral nutrition indications?
…Yes …No
8. Do you think you have enough information about parenteral nutrition indications?
…Yes …No
9. Do you think nutrition is a problem for COVID-19 patients?
…Yes …No
10. Do you question the symptoms that will affect the nutrition of COVID-19 patients? (e.g. nausea, vomiting)
…Yes …No
11. Have you read the publications about nutritional management for COVID-19 patients?
…Yes …No
12. Do you think that nutritional therapy have a beneficial effect on patients' clinical outcomes?
…Yes …No

Table 2. Descriptive Characteristics and Answers to Questions

Characteristics	**N=100 (%)**
Gender (female)	52 (52)
Year of assistantship	
1	16 (16)
2	20 (20)
3	29 (29)
4	25 (25)
5	10 (10)
Have you worked in intensive care before?	86 (86)
Have you done a geriatrics rotation?	68 (68)
Do you find your knowledge about nutrition management competent?	48 (48)
Can you evaluate each patient in terms of nutritional status in your daily clinical practice in inpatient wards?	63 (63)
How often would you like a consultation to clinical nutrition unit for your patients with malnutrition or at risk of malnutrition?	
Sometimes	50 (50)
Often-Always	50 (50)
Do you think you have enough information about enteral nutrition indications?	62 (62)
Do you think you have enough information about parenteral nutrition indications?	55 (55)
Do you think nutrition is a problem for COVID-19 patients?	92 (92)
Do you question the symptoms that will affect the nutrition of COVID-19 patients?	69 (69)
Have you read the publications about nutritional management for COVID-19 patients?	6 (6)
Do you think that nutritional therapy have a beneficial effect on patients' clinical outcomes?	97 (97)

Factors Affecting Awareness and Competence

As expected, the competence about knowledge on nutrition management rised with the increase in research assistantship duration, performing intensive care and geriatrics rotations (respectively p = 0.002, p = 0.001, p <0.001). Ratio of self-competence about enteral nutrition indications increases with the climbing of time spent in research assistants and performing geriatrics rotation (respectively p = 0.02, p = 0.03). Performing geriatrics and intensive care rotations did not make a statistically significant difference in terms of competence about parenteral nutrition indications. Among the answers given to the other survey questions, the time spent as a research assistant, performing intensive care and geriatrics rotations did not significantly affect the answers (Table 3).

DISCUSSION

Malnutrition is a common syndrome in the community and especially in hospitalized patients. Diagnosis of malnutrition that is possible to be treated may be delayed for various reasons. Nutritional evaluation may remain in the background in COVID-19 patients due to other vital problems. The awareness of physicians is important for making the diagnosis without delay and making the necessary intervention. In our study, it was tried to measure the competences and attitudes of research assistants working in the internal medicine department about nutrition.

In the pandemic of COVID-19, patients can have multisystemic involvement, increase in comorbid conditions and great difficulties arise in the management of patients [2]. One of these

Table 3. Factors Affecting Awareness of Nutrition and Competence[a]

	Year of assistantship		*P*	Performing Intensive care department		*P*	Performing Geriatrics department		*P*
	≤2 (N:40)	>2 (N:60)		Yes (N:86)	No (N:14)		Yes (N:68)	No (N:32)	
Do you find your knowledge about nutrition management competent?[b]	10 (20.8)	38 (79.2)	*0.002*	47 (97.9)	1 (2.1)	*0.001*	42 (87.5)	6 (12.5)	*<0.001*
Could you evaluate each patient in terms of nutritional status in your daily clinical practice in inpatient wards?[b]	20 (31.7)	43 (68.3)	*0.25*	57 (90.5)	6 (9.5)	*0.09*	46 (73.0)	17 (27.0)	*0.16*
How often would you like a consultation to clinical nutrition unit for your patients with malnutrition or at risk of malnutrition? (Often-Always)[b]	19 (38.0)	31 (62.0)	*0.68*	42 (84.0)	8 (16.0)	*0.56*	33 (66.0)	17 (34.0)	*0.67*
Do you think you have enough information about enteral nutrition indications?[b]	17 (27.4)	45 (72.6)	*0.02*	56 (90.3)	6 (9.7)	*0.11*	47 (75.8)	15 (24.2)	*0.03*
Do you think you have enough information about parenteral nutrition indications?[b]	15 (27.3)	40 (72.7)	*0.04*	49 (89.1)	6 (10.9)	*0.33*	40 (72.7)	15 (27.3)	*0.26*
Do you think nutrition is a problem for COVID-19 patients?[b]	35 (38.0)	57 (62.0)	*0.25*	79 (85.9)	13 (14.1)	*0.90*	63 (68.5)	29 (31.5)	*0.71*
Do you question the symptoms that will affect the nutrition of COVID-19 patients?[b]	25 (36.2)	44 (63.8)	*0.94*	61 (88.4)	8 (11.6)	*0.30*	46 (66.7)	23 (33.3)	*0.67*
Have you read the publications about nutritional management for COVID-19 patients?[b]	1 (16.7)	5 (83.3)	*0.42*	6 (100)	0 (0)	*0.59*	64 (68.1)	30 (31.9)	*1.00*
Do you think that nutritional therapy have a beneficial effect on patients' clinical outcomes?[b]	36 (37.1)	61 (62.9)	*0.55*	83 (85.6)	14 (14.4)	*1.00*	65 (67.0)	32 (33.0)	*0.55*

[a]The numbers in parentheses represent the percentages of the rows, [b]The number and rate of those who answered yes to the questions are given.

comorbid conditions is malnutrition. Its incidence is increasing, especially in the geriatric age group. Malnutrition was detected in 52.7% of the patients in the study in which malnutrition was evaluated in older COVID-19 patients in China [9). In a study in which patients hospitalized due to COVID-19 in all age groups in France were examined, the malnutrition rate was found to be 42.1% [10]. With appropriate nutritional management, complications are reduced and results are observed to be better [11]. European Society of Parenteral and Enteral Nutrition emphasized the importance of the recognition and correct management of malnutrition in COVID-19 patients. Ten practical recommendations for the nutritional management of this group of patients were presented [4].

Malnutrition -independently from COVID-19- poses a significant problem in Turkey. In Turkey in 2009 in a multicenter study, it was seen that 15% of patients were at risk of malnutrition during hospitalization. In addition, 48.2% of the patients at risk of malnutrition did not receive any nutritional treatment [12]. In order to increase this ratio, it is necessary to give importance to the education of physicians on this subject and to increase their awareness and competence about nutrition. When the education programs are examined, it is aimed that physicians will be able to diagnose, treat, monitor and control malnutrition, also implement preventive measures while graduating from faculty of medicine in the Council of Higher Education Undergraduate Medical Education - National Core Curriculum Program [13]. The same goals are also included in the internal medicine, geriatrics and intensive care curriculums of the Medical Specialty Board [14]. When we look at the globally, it is seen that nutrition does not take place in medical education in a sufficient amount, regardless of the country [15]. As a result of our study, ratio of those who did not consider their knowledge competent in enteral and parenteral nutrition indications was found to be substantially high among the research assistants. These competency ratios increase as rising the research assistantship year, performing the rotations of geriatrics and intensive care. Especially, information about enteral nutrition indications increased after geriatrics rotation. In addition, there are very few resident physicians who read publications for the nutritional management of COVID-19 patients. Research assistants also need to increase their interest about nutrition. There is no study in the literature similar to our study, which attracted attention to nutrition education during the COVID-19 pandemics. Therefore, we could not make a comparison with the data we obtained.

There are problems about nutritional education around the world [16-19]. In the study conducted with questions directed to physicians through a survey in Saudi Arabia, it was observed that the knowledge of physicians on nutrition was insufficient. While physicians think that malnutrition management is moderately relevant to their job, they have also stated that their clinical practice in malnutrition is less [20]. In a study in Canada, physicians denoted the nutritional status of patients should be examined at the time of admission to the hospital, during hospitalization and being discharged, while ratio of those who regularly apply this procedure was found to be quite low [21]. In our study, despite vast majority of research assistants thought that nutrition creates a problem in patients and nutritional support positively affects clinical results, while ratio of research assistants who make daily nutritional evaluations of patients and consultation from the clinical nutrition unit was not sufficient.

Our study has some limitations. Firstly, it was designed as single-center study. So, number of participants limits generalizability of results. Since it is a survey study, the answers of participants are subjective. Also, survey is not a validated survey and created by researchers. However, we have also strong points. Malnutrition remains in the backround in COVID-19 pandemics and we draw attention to this issue in terms of education. The competencies and attitudes of the research assistants about malnutrition, were examined and the deficiencies in this regard were tried to be revealed.

CONCLUSION

Malnutrition is a very common problem in hospitalized patients. The magnitude of this problem has increased with the pandemic of COVID-19. With correct diagnosis and treatment, the negative consequences of malnutrition can be prevented. For this reason, it is of great importance to raise the awareness of physicians on this issue and to include more nutritional education in undergraduate and post-graduate education curriculum.

Author contribution

Study conception and design: SC, ZK, and MGH; data collection: SC, ZK, MGO, and AOB; analysis and interpretation of results: SC, BBD, MC, and MGH; draft manuscript preparation: SC, BBD, MC, and MGH. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Non-interventional Clinical Researches Ethics Board of Hacettepe University Faculty of Medicine (Protocol no. 2021/02-29/19.01.2021).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Age-related Comparison of Hip Joint Morphology in Isolated Femur Neck Fractures

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ABSTRACT

Objective: Femoral neck fractures mostly occurs due to high-energy trauma in young population and management differs compared to elderly. Different geometric parameters in the hip joint can play a role in fracture morphology regarding to the age. Present study aims to compare hip morphology between young and elderly population

Materials and methods: 45 patients with isolated femoral neck fracture included to the study. Patients were divided into two regarding to the age; group 1 (younger than 60 yr.) and group 2 (older than 60 yr.). Garden and Pauwels classifications, Sharp angle (acetabular index-AI), acetabular depth (AD), Hip-axis length (HLA), Neck-shaft angle (NSA), Center-edge angle (CE), Singh indexes and femur head extrusion indexes were compared between groups.

Results: The mean age of group 1 (22 patients) was 48 ± 10.4 while the mean age of group 2 (23 patients) was 77 ± 6.3. Significant differences found in 3 parameters; the mean HLA (13.4 ± 1.4 cm vs 12 ± 1.1 cm) (p: 0,034), the Sharp angle (37.9° ± 5° vs 40.3° ± 3°) (p: 0.047) and the CE (38.1° ± 6.2° vs 34.8° ± 4.5°) (p: 0.48) between group 1 and 2 respectively. No statistically significant difference was found in terms of AD, NSA, Singh index and extrusion index.

Conclusions: Our study shows influence of proximal femoral and acetabular morphology on femoral neck fracture in young patients and may help future studies to reveal the relevance between hip morphology and fractures type.

Keywords: femoral neck fracture, garden, hip axis length.

INTRODUCTION

Femoral neck fractures (FNF) are commonly seen in the elderly patients after a minor trauma [1]. However, they account for only 2-3% of all femoral fractures in adults and may be challenging due to resulting from high-energy trauma [2-4]. Classification of FNF depending on the location includes: subcapital, transcervical and basicervical pattern. Common fracture pattern in adults is transcervical fracture with a vertical orientation and instability accompanied by loss of cortical bone. High risk of nonunion, malunion and avascular necrosis arises due to the complexity of the neck fracture in young population as well [5-7]. Pauwels emphasized the significance of vertical orientation of the fracture in his classification [8]. Subsequent studies about the outcome of vertical fractures have shown greater risk for complications and poor healing as well [5, 9, 10].

Management of FNF in young adults and understanding the differences compared to elderly population is crucial. Arthroplasty procedures are not ideal even in comminuted fractures and several fixation methods have been described. The main goal of the treatment is to preserve native hip joint and to return to high level of activity. Therefore,

a better understanding of the nature of the FNF may improve treatment strategies and decrease complications. A few studies about the relationship proximal femur geometry and fracture pattern especially for intertrochanteric fractures in elderly patients have been performed [11-13]. Increased hip axis length (HAL) and neck shaft angle (NSA) have been found related with osteoporotic FNF [14, 15]. However, there is no consensus about the relevance of hip morphology and fracture type in young population. Paucity of studies performed to further characterize the pathoanatomic properties of the fracture pattern in patients under 60 years of age [9].

Thus, we aimed to determine morphological differences between young and elderly patients. We hypothesized that different geometric parameters can play a role in fracture type regarding to the age.

METHODS

Institutional review board approval was obtained at our institution. 192 patients who underwent surgery for FNF in our clinic between 2009 and 2017 were retrospectively reviewed. Patients with isolated femoral neck fracture were divided into two as group 1 (younger than 60 yr.) and group 2 (older than 60 yr.). Patients who had fracture in contralateral hip and those with pelvic fractures, pathologic fractures, paralysis, lower limb deformities, metabolic bone disease, and surgical history on the same extremity were excluded from the study. 45 of 192 patients who met the criteria were included in the study. The difference between the Garden and Pauwels classifications, Sharp angle (acetabular index-AI), acetabular depth (AD), Hip-axis length (HLA), Neck-shaft angle (NSA), Center-edge angle [10] (Figure 1), Singh indexes and femur head extrusion indexes were assessed on the standard A-P pelvis radiographs (Figure 2). Measurements made on contralateral hip and obturator foramen index was used for standardization of preop and immediate postop AP pelvis radiographs. The picture and Archiving Communication System (PACS) were used to assess radiographic records in all patients.

Statistical analysis was performed using the software package SPSS (IBM Corp Released 2015: IBM SPSS Statistics for Mac US, Version 23.0. Armonk, NY, USA) means, standard deviations (SD), medians and range are used for continuous variables. Normality was assessed using the one-sample Kolmogorov-Smirnov test and analyses of each parameter between groups was performed using the T-test. Parameters with p values less than 0.05 were considered as statistically significant.

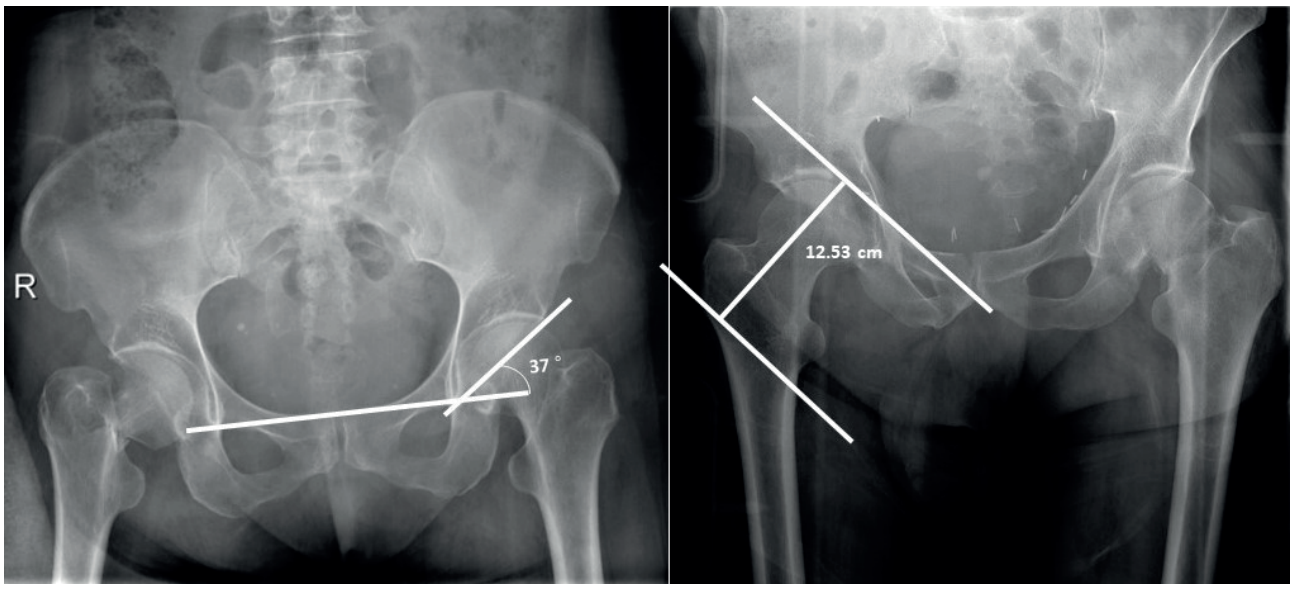

Figure 1. The Sharp angle (also known as acetabular index) is formed between Hilgenreiner line and second line that extends along the acetabular outer corner (a), The hip axis length was measured as a line extending along the femoral axis from the base of the greater trochanter to the inner pelvic rim (b).

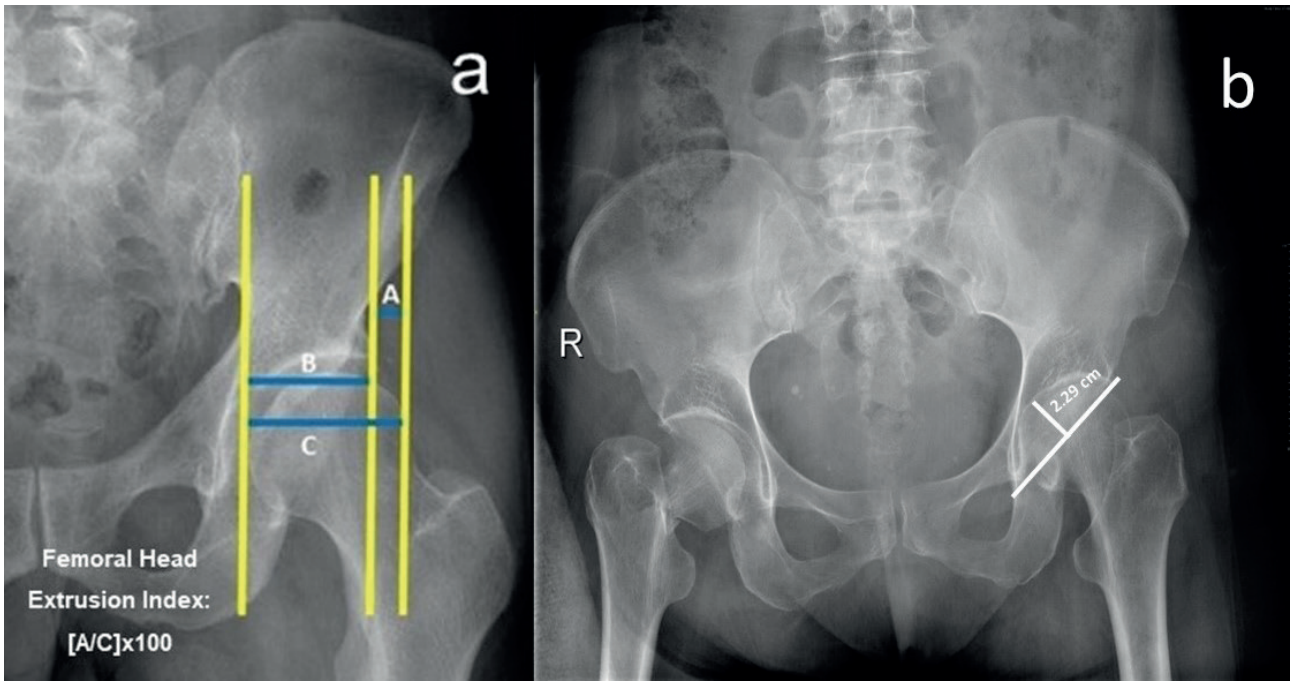

Figure 2. Femoral head extrusion index is measured by dividing the horizontal distance of the lateral femoral head that is uncovered by acetabulum to the total distance or width of the femoral head (a). Acetabular depth was measured by a tangent line is drawn from the most lateral edge of the acetabulum to the teardrop on the same side. A perpendicular line is drawn to the deepest point of the acetabular roof (b). All of the measurements have been made on contralateral healthy hip.

RESULTS

The mean age of group 1 (22 patients) was 48 ± 10.4 while the mean age of group 2 (23 patients) was 77 ± 6.3. There was no significant difference between the two groups in terms of gender. In the group 1: 73% of the fractures were transcervical, 13.6% were basicervical and 13.6% were subcapital. In the group 2: 48.8% of the fractures were subcapital, 46.8% were transcervical and 4.3% were basicervical. 86% of the fractures were displaced in group 1, while 78% of the fractures were displaced in group 2 (p: 0.69) (Table 1). 68.2% (15 patients) of the fractures were Pauwels type 3 in group 1 and only 2% of the fractures (2 patients) were classified as Pauwels type 3 in the group 2 (p:0.001).

We found statistically significant differences in the mean HLA (13.4 ± 1.4 cm vs 12 ± 1.1 cm) (p: 0,034), the Sharp angle (37.9° ± 5° vs 40.3° ± 3°) (p: 0.047) and the CE (38.1° ± 6.2° vs 34.8° ± 4.5°) (p: 0.48) between group 1 and 2 respectively. No statistically significant difference was found in terms of AD, NSA, Singh index and extrusion index. Table 2 demonstrates radiological results between groups.

Table 1. Demographics of the study groups.

	Group 1 (<60 yr.)	Group 2 (>60 yr.)	P Value
Number of Patients	22	23	
Mean Age	48±10.4	71±6.2	**<0,001**
Gender (Male/Female)	13/9	11/12	0,647
BMI	23.3±4.3	22.6±5.4	0,434
Location			
-Subcapital	%13.6	%48.8	
-Transservical	%72.7	%47.8	**0,03**
-Basiervical	%13.6	%4.3	
Garden 3&4 (n.o patients)	%86.4 (19)	%78.3 (18)	0,69

Table 2. Results of radiological parameters between groups.

	Group 1 (<60 yr.)	Group 2 (>60 yr.)	P value
Acetabular Index	37.8° ± 4.6°	40.3° ± 3.4°	**0.047**
Acetabular Depth	1,06 ± 0.3	1±0.2	0.344
Hip Axis Length	13 ± 1.4 cm	12.2 ± 1.1 cm	**0.034**
Neck-Shaft Angle	134.5° ± 5°	132.2° ± 5.2°	0.134
Lateral-Central Edge Angle	38.1° ± 6.2°	34.8° ± 4.5°	**0.048**
Singh Index	5.7 ± 0.5	2.6 ± 1.1	<0.001
Extrusion Index	12.3 ± 4.3	11.9 ± 6.4	0.783

DISCUSSION

There are several approaches preferred by the surgeons for the treatment of FNF in young patients. After Pauwels pointed out the importance of vertical orientation, many studies using computed tomography (CT) as well revealed the relationship between intraarticular complex lower limb fractures pathoanatomy and the fracture type. FNF in younger patients mostly occurs from high-energy trauma. Injury pattern in this individuals is a transcervical vertical fracture extending toward the medial calcar and lesser trochanter. The injury occurs due to strong displacement forces across the hip that may lead to failure of fixation and malunion with overall complication rates ranging from 20%-80%. The reason for the difference between the two groups in terms of Garden and Pauwels classification can be predicted as the younger patients having more vertical and unstable fractures as a result of high-energy trauma. [16, 17]. Understanding the morphology and geometry of the both native hip joint and fracture may help explain high complication and failure rates seen of vertical neck fractures in patients under the age of sixty years.

Several studies comparing osteoporotic hip fractures regarding bone quality, age and morphology have been performed previously. Most of them assessed the proximal morphology as an important factor for determining the fracture type [9, 18, 19]. Cory et al. investigated the fracture morphology of high shear angle vertical neck fractures in young adult patients under age of fifty years and vertical coronal fractured averaged 60 degrees and axial fracture obliquity averaged 24 degrees with deficiency in the posterior neck. They stated that major femoral neck comminution was identified in 96% of cases [9]. Maeda et al. compared the femoral morphology and bone mineral density between FNF and trochanteric fractures and found no significant differences of bone mineral density between groups. However, they stated that patients with trochanteric fractures showed a smaller neck shaft angle and smaller cortical index at the isthmus compared to patients with femoral neck fractures [20]. Recently, Rotem et al. studied about hip morphology whether it is influencing the anatomic location of hip fractures in elderly patients. They found significant higher NSA, shorter HLA and a narrower femoral neck diameter in extracapsular fractures compared to the intraarticular ones. The authors concluded that proximal femoral geometry were found to correlate with the location of hip fractures [12]. Additionally, Frost et al. also evaluated the influence of acetabular and femoral versions on fractures of the femoral neck and found no correlation between proximal femur fracture type and acetabular or femoral version [21].

HAL was defined for the first time by Faulkner et al. and he reported increased values were relevant with the risk of hip fracture [13]. Subsequent studies showed that increased HAL was more related with FNF and no relationship found with intertrochanteric fractures. Increased in the HAL proves a higher distance between the center of the hip and lateral part of the femur. Therefore, it represents increase of the load on femoral neck. In our study, HAL was found statistically higher in young patients with more vertical fractures as well. Our study evaluates these radiological parameters between the location of femoral neck fractures in age-related cohorts. Preliminary results of our cohort may help future studies in this regard.

There are some limitations of our study as well; Patients were evaluated retrospectively, CT scans were performed on patients deemed suitable by the emergency department, therefore we couldn't be able to evaluate the whole study group with tomography. Additionally, the study did not assess the influence of injury mechanism over the FNF type. Furthermore, this cohort has a small sample size which could lead to the possibility of a type 2 error. However, to our knowledge this is the first study comparing morphological differences of neck fractures between young and elderly patients. Thus, our findings may help to reveal whether geometrical parameters influence the type and location of the FNF in future studies with larger cohort. Since this study only presented radiological measurements, further studies are needed to evaluate the clinical usefulness of the study findings.

CONCLUSION

This study reveals the influence of proximal femoral and acetabular morphology on FNF between young and elderly patients. Increased HAL and CE might be associated with neck fractures in young population. These findings might provide baseline information for further studies.

Author contribution

Study conception and design: SK, SB, and BA; data collection: SK, and SB; analysis and interpretation of results: SK, SB and OC; draft manuscript preparation: SK, BA, and AMT. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Ethical approval was obtained from the Hacettepe University Faculty of Medicine local ethics committee (GO 22/1030).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Evaluation of Risk Factors Affecting Progression in Primary Open-Angle Glaucoma and Exfoliation Glaucoma in a Turkish Population

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ABSTRACT

Objective: To evaluate the effects of risk factors on progression in primary open-angle glaucoma (POAG) and exfoliation glaucoma (XFG).

Materials and methods: The study included 139 patients with POAG and XFG followed up at Hacettepe University Faculty of Medicine, Department of Ophthalmology, Glaucoma Unit. A number of factors were evaluated through a cross-sectional design for all the patients, including age, sex, hypertension, diabetes, thyroid disease, cardiovascular disease, migraine, alcohol, smoking, family history, affected side, lens status, central corneal thickness (CCT), number of medications, body mass index (BMI), cup-to-disc (C/D) ratio, intraocular pressure (IOP), computerized automated visual field mean deviation (MD), and prior surgery.

Results: The patients were divided into two groups, POAG and XFG, and further divided into the following two subgroups: progressive and non-progressive. Of the patients, 75 (53.9%) had POAG, and 64 (46.1%) had XFG. In the patients followed up, annual MD change was 0.96 ± 1.5 dB/year, baseline MD was −5.06 ± 5.61 dB, and IOP was 15.94 ± 1.93 mmHg. Potential risk factors for progression in the whole group were evaluated, but no significant difference was found between the groups with and without progression for all factors. Subgroup analysis revealed that in the POAG group, BMI was significantly higher in the non-progressive disease subgroup (p=0.01); furthermore, in the XFG group, IOP was significantly higher in the progressive disease subgroup (p=0.02). According to multiple logistic regression analysis, a 1-unit decrease in BMI in the POAG group increased the risk by 1.3 times (p=0.01), and smoking in the XFG group resulted in a 6-fold reduction in the risk of progression (p=0.04).

Conclusion: Although mean IOP was higher in XFG group, the present study found BMI in POAG and smoking in XFG as independent factors that reduced progression in our series.

Keywords: primary open-angle glaucoma, exfoliation glaucoma, progression, risk factors.

INTRODUCTION

Glaucoma is a leading cause of irreversible blindness and affects more than 60 million people worldwide. Although it is a multifactorial disease, its etiopathogenesis has not been fully elucidated. Intraocular pressure (IOP) is the most important identifiable risk factor implicated in the development and progression of the disease, and a decrease in IOP does not definitively prevent progression [1]. Progression may also occur in patients with low IOP. Primary open-angle glaucoma (POAG) is the most common type of glaucoma and occurs without any underlying trauma, inflammation, or secondary eye disease. Main risk factors are high IOP, age, race, and family history [2]. Exfoliation Syndrome (XFS) is an important ocular manifestation of a systemic disease and is the most common cause of secondary open-angle glaucoma [3,4]. In these patients, mean IOP is higher, and glaucomatous optic neuropathy and coronary artery disease are more relatively common [3,4]. Compared to POAG, it progresses more rapidly and requires a more aggressive treatment. There are inconsistent results regarding the risk factors affecting the progression of glaucoma in the literature. The aim of this study was to evaluate the effect of potential risk factors on progression in patients with POAG and Exfoliation Glaucoma (XFG).

MATERIALS AND METHODS

We included 139 patients with POAG and XFG followed between January 2013 and March 2017 at Hacettepe University Faculty of Medicine, Department of Ophthalmology, Glaucoma Unit. Ethics committee approval for the study was obtained from Hacettepe University Non-Invasive Clinical Research Ethics Committee, approval no GO 17/389 of 16.05.2017. This study was conducted in accordance with the tenets of the Declaration of Helsinki. Medical records of patients who were followed regularly for the last 3 years for POAG and XFG and who underwent at least 5 visual field tests were screened to extract and record systemic findings, diseases, ocular findings, and diagnostic test results. Height and weight measurements were performed using a digital measuring device (Seca 767+220, Seca GmbH, Hamburg, Germany) during patient visits for glaucoma. These parameters were compared in groups with and without progression based on and regardless of the type of glaucoma. Patients were included in the study if they had a regular follow-up of at least 3 years with a diagnosis of POAG or XFG, and they were excluded if they had an eye disease such as uveitis, scleritis, herpetic eye disease, and diabetic retinopathy. Reliable visual field test criteria were a false positive and negative rate and fixation loss of <30% and <20%, respectively [5,6]. Glaucoma staging was performed using Hodapp-Parrish-Anderson criteria based on visual field loss [7].

Visual acuity, cup/disc (C/D) ratio and CCT were evaluated based on data from 3 years ago; IOP and number of medications were evaluated based on mean numbers. Smoking was considered positive if patients smoked at least 1 cigarette per day for 1 year. Cardiovascular diseases considered for evaluation included hypercholesterolemia, hypertriglyceridemia, ischemic and valvular heart disease, transient ischemic attack, arrhythmia, heart failure, and peripheral vascular, cerebrovascular, and thromboembolic diseases. Furthermore, we recorded whether the patients used alcohol regularly for the last 1 year or longer. The patients were based on progressive and non-progressive disease in the whole group (Table 1), as well as in the POAG (Table 2), and XFG (Table 3) group. The criterion for progression was a change in MD value by ≥1 dB/year. The worse eye of the patients (the eye more affected by glaucoma) was used in evaluation. Visual field values were obtained from the standard automated perimeter (Humphrey Field Analyzer 2, Carl Zeiss Meditec, Jena, Germany). The visual field test administered to all patients was the 24-2 SITA Standard method.

All statistical analyses were performed on IBM SPSS Statistics 23.0 program. The Kolmogorov–Smirnov test was used to check whether the numerical variables were normally distributed or not. Descriptive statistics were given in mean and standard deviation for normally distributed variables, and in median (minimum–maximum) values for non-normally distributed variables. Two sets of numerical data were compared using the t-test of significance for the difference between the two means for normally distributed variables, the Mann–Whitney U test for non-normally distributed variables, and the Chi-square test (Pearson, Yates

corrected) or Fisher exact test for comparing categorical variables.

Multiple logistic regression analysis was performed to examine the effects of independent variables such as age, sex, hypertension, diabetes, thyroid disease, cardiovascular disease, migraine, alcohol, smoking, family history, affected side, lens status, number of medications, body mass index (BMI), and IOP on the risk of progression. Backward stepwise (Wald) method was used to remove non-significant terms from the model. Odds ratios and confidence intervals were calculated as a result of the analysis. Statistical significance was set at $P<0.05$.

RESULTS

The mean age of the 139 patients included in the study was 68.84 ± 10.6 years (37–92 years). 67 (48.2%) of the patients were male and 72 (51.8%) were female. Risk factors were evaluated comparatively for the progressive and non-progressive disease groups regardless of the glaucoma type, and for the progressive and non-progressive disease subgroups in the POAG and XFG groups. A total of 31 patients (41.3%) in the POAG group and 33 patients (51.5%) in the XFG group had progressive disease. Statistical analyses were performed on the eyes of patients with progressive disease. The whole group assessment found a median (minimum–maximum) value of –0.76 (–7.12–4.97) dB for annual MD change, a mean (±SD) value of –5.06 ± 5.6 dB for baseline MD, and a mean (±SD) value of 15.94 ± 1.9 mmHg for IOP. According to the Hodapp-Parrish-Anderson Classification, 105 patients were in Stage 1, 18 patients in Stage 2, 8 patients in Stage 3 and 8 patients in Stage 4 [7].

In patients with XFG, the median (minimum–maximum) value for mean IOP was 16 (10–19) in the progressive disease group and 16 (13–18) in the non-progressive disease group (p=0.02). In the POAG group, the median (minimum–maximum) value for BMI was 25.7 (18.6–30.2) in the progressive disease group and 26.7 (21.2–36.9) in the non-progressive disease group (p=0.01). According to multiple logistic regression analysis, a 1-unit decrease in BMI in the POAG group increased the risk by 1.3 times (p=0.01), and smoking led to a 6-fold reduction in the risk (p=0.04). Other evaluated factors had no significant effect on progression in glaucoma. Table 1 shows the results for the whole group of patients. Table 2 and Table 3 show the results of the subgroup analyses for patients with POAG and XFG.

DISCUSSION

In glaucoma, knowledge of systemic and ocular risk factors that may affect progression provides a significant contribution to designing the treatment plan and follow-up of patients. Several have investigated glaucomatous progression, and most have highlighted MD change as a criterion. The authors observed that these studies, essentially based on pointwise linear regression analysis, found an annual change of 1 dB to have high specificity and sensitivity for glaucomatous progression regardless of the stage of the disease, and they evaluated progression on the basis of these studies [8,9].

In the present study, we found that mean IOP in the XFG group was higher in the progressive disease group; BMI in POAG and smoking in XFG emerged as independent risk factors with negative relationship with glaucomatous progression. Some studies in the literature investigating risk factors have reported that IOP affects progression, as observed in our study. Leske et al. showed that a 10%–19% decrease in IOP was effective in slowing down progression [10]. Another study with 557 patients with POAG and XFG reported that mean IOP and more intensive treatment were associated with progression [11]. In a study with 167 patients with XFG, Konstas et al. showed mean IOP to be associated with progression, with a progression rate of 28% for ≤17 mmHg, 43% for 18–19 mmHg, and 70% for ≥20 mmHg [12]. A study by Hollo et al. with 134 patients with XFG reported progression at a rate of 40% at ≤17 mmHg, and 70% at >17 mmHg [2]. Another study by Hollo et al. with 201 patients with XFG showed progression to occur at a rate of 33% for ≤13 mmHg, 54% for 14–21 mmHg, and 84% for ≥22 mmHg [13]. Our study concluded that mean IOP in the XFG group was significantly higher in the progressive disease group, but evaluation for both the POAG and the whole group revealed no significant intergroup differences in terms of mean IOP.

Many studies in the literature mentioned the protective effect of increased BMI in POAG and

Table 1. Comparison of risk factors for the whole group

	Non-progressive (n=75)	Progressive (n=64)	p value
Mean Age (±SD)	66.7 ± 10.9	70.4 ± 10	0.40
Mean CCT (±SD)	540.7 ± 43.2	529.6 ± 35.7	0.10
Sex			
Male	34 (%45.3)	33 (%51.5)	0.46
Female	41 (%54.6)	31 (%48.5)	
Hypertension	43 (%57.3)	37 (%57.8)	0.95
Diabetes	25 (%33.3)	15 (%23.4)	0.27
Thyroid disease	12 (%16)	6 (%9.37)	0.36
Cardiovascular disease	24 (%32)	24 (%37.5)	0.61
Migraine	5 (%6.66)	2 (%3.1)	0.40
Alcohol consumption	10 (%13.3)	6 (%9.3)	0.64
Smoking	16 (%21.3)	10 (%15.6)	0.52
Positive family history	24 (%32)	18 (%28.1)	0.75
Affected side			
Unilateral	10 (%13.3)	11 (%17.1)	0.69
Bilateral	65 (%86.7)	53 (%82.9)	
Lens			
Phakic Patient	58 (%77.3)	41 (%64)	0.12
Pseudophakic Patient	17 (%22.7)	23 (%36)	
Number of Medications (median-min-max)	1.0 (0-4)	2.0 (0-4)	0.06
BMI (median-min-max)	25.8 (20.3-40)	25.8 (18.3-33.5)	0.5
C/D ratio (median-min-max)	0.4 (0.2-0.8)	0.5 (0.2-1)	0.36
Mean IOP (median-min-max) mmHg	16 (13-18)	16 (10-25)	0.65
History of surgery			
Cataract extraction	15 (%20)	17 (%26.5)	0.17
Trabeculectomy	6 (%8)	8 (%12.5)	
No surgery	52 (%69.3)	33 (%51.5)	
Cataract extraction and trabeculectomy	2 (%2.66)	6 (%9.3)	

suggested various mechanisms to explain this [14-19]. In a large-series study involving 787777 women and 41352 men, Pasquale et al. evaluated the association between anthropometric measurements and the incidence of POAG, and showed higher BMI in women to be associated with lower incidence of POAG, but they could not find the same association in men [14]. Adipose tissue can act as an endocrine organ and secrete paracrine factors that can affect the death of retinal ganglion cells [20]. One possible mechanism that has been suggested is that increased estrogen in circulation in people with high BMI binds to receptors in retinal ganglion cells and exerts a protective effect [21]. However, the Singapore Eye Study showed low BMI to be associated with a large vertical C/D ratio in men [22]. The Barbados Eye Study found higher BMI in men and women to have protective effects against the risk of POAG, and suggested this might be due to genetic differences in people with higher BMI [23]. Gasser et al. found that people with lower BMI had an increased predisposition to developing glaucoma [24]. Similarly, Zheng et al. and Xu et al. reported that people with a predisposition to glaucoma were tall people with low BMI [15,16]. Springelkamp et al. showed that tall, thin, and low-BMI people had a greater C/D ratio and a smaller neuroretinal rim area, and in parallel with other studies, they showed increased BMI to be a protective factor for POAG [17]. Trans-lamina cribrosa pressure results from the difference between IOP and cerebrospinal fluid (CSF) pressure, and its increase is associated with glaucomatous nerve damage in the optic disc [18]. Since BMI is correlated with CSF pressure, low CSF pressure and low BMI are thought to be involved in the pathogenesis of glaucomatous optic neuropathy [18,19]. In parallel with this information, two

Table 2. Comparison of risk factors in the Primary Open-Angle Glaucoma group

	Non-progressive (n=44)	Progressive (n=31)	p value
Mean Age (±SD)	63.43 ± 11.44	67.29 ± 10.78	0.14
Mean CCT (±SD)	549.75 ± 43.60	533.54 ± 33.19	0.86
Sex			
Male	19 (%43.1)	11 (%35.4)	0.66
Female	25 (%56.9)	20 (%64.6)	
Hypertension	24 (%54.5)	16 (%51.6)	0.98
Diabetes	13 (%29.5)	7 (%22.5)	0.68
Thyroid disease	8 (%18.1)	4 (%12.9)	0.75
Cardiovascular disease	15 (%34)	11 (%35.4)	0.83
Migraine	4 (%9)	2 (%6.5)	0.51
Alcohol consumption	5 (%11.3)	1 (%3.2)	0.39
Smoking	5 (%11.3)	1 (%3.2)	0.39
Positive family history	19 (%43.1)	13 (%41.9)	0.89
Affected side			
Unilateral	5 (%11.3)	4 (%12.9)	0.87
Bilateral	39 (%88.7)	27 (%87.1)	
Lens			
Phakic Patient	34 (%77.2)	21 (%67.7)	0.51
Pseudophakic Patient	10 (%22.8)	10 (%32.3)	
Number of Medications (median-min-max)	1 (0-2)	1 (0-4)	0.41
BMI (median-min-max)	26.7 (21.2-36.9)	25.7 (18.6-30.2)	**0.01***
C/D ratio (median-min-max)	0.4 (0.2-0.8)	0.5 (0.2-1)	0.35
Mean IOP (median-min-max)	16 (13-18)	16 (12–25)	0.13
History of surgery			
Cataract extraction	10 (%22.7)	7 (%22.5)	0.13
Trabeculectomy	2 (%4.5)	3 (%9.6)	
No surgery	32 (%72.7)	18 (%58)	
Cataract extraction and trabeculectomy	0 (%0)	3 (%9.6)	

studies by Berdahl et al. showed that CSF pressure was lower in patients with POAG compared to the control group, and stated that low CSF pressure may have the same effect as increased IOP in the development of glaucoma [25,26]. Although there is no data in the literature evaluating progression in connection with BMI in POAG and XFG patients; our study showed that low BMI was associated with progression of glaucoma in patients with POAG, but could not demonstrate the same association in patients with XFG, which might be attributable to the different mechanisms involved in the development of the two glaucoma subtypes. New research supports the hypothesis of presence of a paravascular pathway in the eye, similar to the recently discovered "glymphatic system" of the brain, a functional waste clearance pathway that promotes the removal of solutes, including amyloid-β, from the brain through paravascular channels. This discovery has provided a different and strong insight into the pathophysiology of the disease [27]. Amyloid-β increases with chronic elevation in IOP in animals with experimentally induced ocular hypertension and causes the death of retinal ganglion cells [28]. Lower CSF pressure and increased trans-lamina cribrosa pressure gradient lead to restriction in normal glymphatic flow at the level of lamina cribrosa, possibly resulting in accumulation of toxic substances such as amyloid-β. These mechanisms strongly support the association between low BMI and progression in POAG.

Vascular factors are thought to be involved in the pathogenesis of glaucoma owing to changes in blood flow in the optic nerve head. Although some studies have shown that smoking is associated with the development of glaucoma,[29] other studies

Table 3. Comparison of risk factors in the Exfoliation Glaucoma group

	Non-progressive (n=31)	Progressive (n=33)	p value
Mean Age (±SD)	71.3 ± 8.4	71.3 ± 8.4	0.33
Mean CCT (±SD)	528 ± 40	528 ± 40	0.83
Sex			
Male	15 (%48.3)	15 (%48.3)	0.22
Female	16 (%51.7)	16 (%51.7)	
Hypertension	19 (%61.2)	19 (%61.2)	0.94
Diabetes	12 (%38.7)	12 (%38.7)	0.32
Thyroid disease	4 (%12.9)	4 (%12.9)	0.66
Cardiovascular disease	9 (%29)	9 (%29)	0.54
Migraine	1 (%3.2)	1 (%3.2)	0.48
Alcohol consumption	5 (%16.1)	5 (%16.1)	0.81
Smoking	5 (%16.1)	5 (%16.1)	0.81
Positive family history	5 (%16.1)	5 (%16.1)	0.81
Affected side			
Unilateral	5 (%16.1)	5 (%16.1)	0.84
Bilateral	26 (%83.9)	26 (%83.9)	
Lens			
Phakic Patient	24 (%77.4)	24 (%77.4)	0.23
Pseudophakic Patient	7 (%22.6)	7 (%22.6)	
Number of Medications (median-min-max)	1 (0-3)	1 (0-3)	0.12
BMI (median-min-max)	25.3 (20.3-40.0)	25.3 (20.3-40.0)	0.22
C/D ratio (median-min-max)	0.5 (0.3-0.8)	0.5 (0.3-0.8)	0.06
Mean IOP (median-min-max)	16 (13-18)	16 (13-18)	**0.02***
History of surgery			
Cataract extraction	5 (%16.1)	5 (%16.1)	0.73
Trabeculectomy	4 (%12.9)	4 (%12.9)	
No surgery	20 (%64.5)	20 (%64.5)	
Cataract extraction and trabeculectomy	2 (%6.4)	2 (%6.4)	

have found no association [30,31]. Furthermore, association between smoking and progression in glaucoma is controversial in the literature, and data are scarce on this issue. Asaoka et al. argued that there is a positive correlation between smoking and progression in glaucoma in patients with POAG, and showed that visual field damage in smoking patients with POAG was more pronounced in the lower quadrant, similar to non-arteritic anterior ischemic optic neuropathy [32]. Chiotoroiu et al. reported that glaucoma progressed faster in smokers, without specifying which type of glaucoma patients were included in the study [33]. However, the newly published UK Glaucoma Treatment study showed that glaucomatous damage in the visual field decreased with active or previous smoking in patients with POAG and XFG [34]. This is possibly the first study that included patients with XFG and evaluated glaucomatous progression in connection with smoking, and its results are in line with our study [34] The UK Prospective Diabetes Study demonstrated that smokers have a lower incidence of retinopathy and a lower risk of retinopathy progression compared to non-smokers [35]. The researchers in that study emphasized that the strength of the association alone was unlikely to be a coincidence, and that nicotine itself or one of the many other active compounds found in tobacco smoke may have an independent effect. Hollo, however, reported that smoking did not have an acute effect on peripapillary and macular vessel density in middle-aged smokers [36]. These data are supported by the Nurses' Health Study and the Health Professionals Follow-up Study that found an inverse correlation between pack-year and incidence of glaucoma, in line with our findings [37]. Unadjusted analysis in the National Health and Nutrition Examination Survey reported that current

smokers had a lower odds of glaucoma compared to non-smokers and ex-smokers, but this association lost statistical significance in the adjusted models [38]. The authors hypothesized that the possible protective effects of smoking could be negated by heavy smoking [38]. In addition, there appears to be an inverse dose-response relationship between Parkinson's disease and smoking, which is supported by meta-analyses [39]. The protective effect of smoking on neurodegenerative diseases including glaucoma should not be underestimated. Despite the known adverse effects of smoking or nicotine on ocular circulation and tissues, nicotine is also thought to have protective mechanisms on the blood supply of the optic nerve. Nicotine may cause the release of nitric oxide from perivascular nitric oxide (NO)-dependent nitrergic neurons, leading to vasodilation [40] A case-control study based on data from the Nurses' Health Study and the Health Professionals Follow-Up Study showed that smoking has an effect on glaucoma associated with nitric oxide synthase 3 (NOS3) gene variations [41]. Although XFG is known to be associated with molecules that affect NO-dependent pathways such as sirtuin, apelin and asymmetric diarginine,[42,43] smoking, which increases NO production, can be expected to affect the progression in XFG. If the inverse correlation between smoking and XFG is to be confirmed, further research into the mechanisms involved could provide a better understanding of the disease and ultimately help us identify treatment targets. Although the protective effect of not smoking is consistent with some epidemiological evidence for glaucoma and other types of neurodegeneration, the evidence is mixed and complex. Therefore, additional research could help clarify associations.

Cataract surgery in eyes with POAG and XFG is known to cause significant changes in anterior segment parameters such as IOP, CCT, anterior chamber depth, and number of endothelial cells [44,45] The effects of these factors on progression in patients with POAG and XFG have been evaluated in numerous studies in the literature [1,2,10,13,32,46]. Our study found no significant difference between the groups in terms of age, sex, hypertension, diabetes, thyroid disease, cardiovascular disease, migraine, alcohol use, family history, affected side, CCT, number of medications, and previous surgery. In a study with 134 patients with XFG, Hollo et al. achieved results similar to those in our study and found no significant difference between the groups with progressive and non-progressive disease in terms of cardiovascular disease, HT, diabetes, age, and sex [2]. In that study, progression was determined based on clinician's evaluation rather than on quantitative values (thinning of the neuroretinal rim, glaucomatous visual field loss, total cupping, diffuse visual field loss, decrease in best-corrected visual acuity) [2]. In the Early Manifest Glaucoma Trial, however, examination of 126 patients with open-angle glaucoma found that age, bilateral disease, exfoliation, cardiovascular disease, and IOP were risk factors for progression, and thinning of CCT caused increased risk of progression in patients with high IOP [10]. However, CCT has been found to have no significant effect in the previously published Early Manifest Glaucoma Trial [1] This has been thought to be related to the small number of patients with progressive disease included in the former study [1]. In the Early Manifest Glaucoma Trials, all cases of open-angle glaucoma were evaluated in the same group, and the presence of exfoliation was considered as a parameter. In both of these studies, age of >68 years was considered a risk factor for progression [1,10]. In the study by Konstas et al. with 167 patients with XFG, however, multivariate analysis revealed that C/D ratio at the time of diagnosis, number of trabeculectomies and mean IOP were correlated with progression [12]. In that study, similar to the aforementioned study by Hollo et al.,[2]. progression was evaluated based on clinical criteria. The study by Asaoka et al. investigated the effects of age, mean IOP, HT, migraine, presence of family history, and smoking on progression in glaucoma, and found that only age and smoking had an effect on progression [32]. Another study by Hollo et al. showed that age, sex, visual acuity, and presence of cardiovascular disease had no effect on progression, which is in line with our study [13].

The most important limitation of our study is the limited number of patients included in this study and the retrospectively design of evaluation. Adequate data could not be extracted from the records about presence of disc hemorrhage and detailed smoking history consisting of the number of cigarettes smoked per day or information as to whether patients smoked regularly during the evaluation period. Refractive errors and differences in axial length can affect the visual field, but these parameters could not be evaluated owing to the lack of fully adequate data in the records.

In conclusion, our study determined that mean IOP in the XFG group was higher in the progressive disease group. It also found BMI in POAG and smoking in XFG as independent factors with a protective effect on progression of glaucoma. Different parameters have been used in studies as criteria for progression, and different results have been achieved in terms of risk factors affecting progression. This difference in results might have been caused by factors such as genetics, population included in the study, differences in follow-up, and differences in drug compliance; these factors should be evaluated more extensively in larger series.

Author contribution

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

Ethical approval

The study was approved by the Hacettepe University Non-interventional Clinical Researches Ethics Board (Protocol no. GO 17/389 / 16.05.2017).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

COVID-19 Fear and Anxiety in Patients with Diabetes Mellitus and their Effect on HbA1c

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ABSTRACT

Objective: To determine the severity of fear and anxiety of COVID-19 in diabetic patients and to evaluate their relationship with HbA1c.

Materials and methods: Between December 2020 and March 2021, a total of 249 patients were included in the study. Demographic characteristics, duration of diabetes, glycosylated hemoglobin A1c (HbA1c) values of the patients were recorded. Fear and anxiety related to COVID-19 were evaluated with the validated Turkish version of the Fear of COVID Scale (FCS) and Coronavirus Anxiety Scale (CAS). FCS and CAS were compared between the diabetic group and the control group. The relationship between FCS and CAS and HbA1c, diabetes year, age, gender, educational status, place of residence, and employment status was investigated.

Results: Median level of HbA1c and duration of diabetes mellitus were 7.65% (range 5.4-13.6) and 10 years (range 1-32) respectively. FCS was higher in the diabetic group compared to the control group (p=0.025). There was no significant difference between the diabetic and control groups regarding CAS. There was no relationship between HbA1c and FCS and CAS (p=0.919, r=0.008, p=0.725, r=0.027, respectively). Anxiety was higher in females than males in diabetic groups (p=0.009).

Conclusions: The fear of COVID-19 is higher in diabetic patients compared to the general population. There was no relationship between fear and anxiety of COVID-19 and HbA1c. However, to protect long-term mental health, there should be strategies to detect and reduce the anxiety and fear caused by the pandemic in the services for diabetic patients.

Keywords: COVID-19, diabetes mellitus, fear, anxiety, HbA1c.

INTRODUCTION

All available data suggested that COVID-19 affects the patients with chronic comorbid diseases more than those without. Diabetes mellitus is one of the comorbid diseases that increase mortality in COVID-19 infection [1]. Being part of the high-risk group, COVID-19 has caused anxiety in diabetic patients [2].

COVID-19 pandemic and social isolation can affect mental health parameters in patients with diabetes mellitus [3]. Psychological distress can increase depressive symptoms in endocrinological comorbid diseases and cause the negative consequences of diabetes mellitus [4-6]. Fear of getting coronavirus infection and running out of diabetes medications, the inability to manage hypoglycemia or hyperglycemia, the fear of not reaching the doctor, the decrease in social support from family and friends due to quarantine caused high anxiety and depression symptoms among diabetic patients [2,7]. Glycemic control can be affected by changes in behavior patterns, daily life, exercise, and increased stress and anxiety [8-11].

In our study, the severity of fear and anxiety of COVID-19 in diabetic patients were determined, and its relationship with HbA1c was investigated. The primary endpoint of our study was to determine COVID-19 fear and anxiety in patients with diabetes mellitus. The secondary endpoint was to determine the effect of COVID-19 anxiety and fear on HbA1c.

MATERIALS AND METHODS

Local ethics committee approval Amasya University Ethical Commitee of Non-Invasive Clinical Research (Date: 12.11.2020, No: 119) was obtained. The study was conducted in accordance with the Declaration of Helsinki.

Between December 2020 and March 2021, adult patients with type 1 and type 2 diabetes were enrolled in the study. Patients under 18 years of age, history of antidepressant use, previous history of psychiatric disease, history of cerebrovascular disease, stage 3-4 heart failure, kidney and liver failure, chronic obstructive pulmonary disease, and malignancy were excluded from the study.

Verbal consent was obtained from the patients before the questionnaire was administered. Age, gender, educational status (“uneducated/primary school” and “middle school or higher”), place of residence (“town/village” and “province/district”), employment status, duration of diabetes, and HbA1c values of the patients were recorded. COVID-19 related fear and anxiety were evaluated by the Turkish validated version of The Fear of COVID scale (FCS) and Coronavirus Anxiety Scale (CAS), respectively [12,13]. HbA1c was studied with high-performance liquid chromatography (Adams A1c HA-8180V). FCS and CAS scores were analyzed according to demographic characteristics and HbA1c values.

The Fear of COVID Scale (FCS): This scale was developed by Ahorsu et al., and adapted to the Turkish context by Satici et al. and Bakioglu et al. [12,14,15]. It is a unidimensional scale with seven items. It has a 5-point Likert-type rating system (ranging from 1: Strongly disagree to 5:Strongly agree). Each question was scored between 1-5. The total score calculated range between 7 and 35. The total score obtained from all scale items reflects the level of fear of coronavirus (COVID-19) experienced by the individual.

Coronavirus Anxiety Scale (CAS): This scale was developed by Lee et al. and adapted to the Turkish context by Evren et al. (13, 16). 5 questions reflecting the frequency of symptoms during the previous two weeks were graded from 0 (never) to 4 (almost every day). This scaling format is consistent with the intersecting symptom scale of DSM-5. If CAS > 9, with 90% sensitivity and 85% specificity, it can distinguish individuals with and without dysfunctional anxiety. A CAS score of 9 and above indicates dysfunctional anxiety associated with the coronavirus. Clinical consideration should also be given when interpreting CAS results.

Statistical Analysis

SPSS 18 (Statistical Package for Social Sciences) software was used for data analysis. The distribution of continuous parameters was evaluated by Kolmogorov-Smirnov and Shapiro-Wilks tests. For normally distributed continuous parameters, groups were compared with independent samples t-test, whereas Mann-Whitney U Test was used to compare non-normally distributed continuous parameters. Nominal parameters were analyzed by the chi-square test and Fisher’s exact test.

Spearman's Rho correlation analysis was used to evaluate the relationship between age, HbA1c, duration of diabetes, and FCS score and CAS score in the diabetic group and was used to evaluate the relationship between FCS score and CAS score and age in all patients (diabetic group and control group). Statistical significance was accepted at $p<0.05$.

RESULTS

Two hundred forty-nine patients (168 diabetic patients and 81 control groups) were included in the study. The demographic data of the diabetic and control group were shown in Table 1. The median pandemic HbA1c and duration of diabetes were 7.65% (range 5.4-13.6) and ten years (range 1-32), respectively. The pre-pandemic HbA1c (median 7.95% (5.2-12.5)) levels were significantly different from pandemic HbA1c (7.65% (5.4-13.6) levels in the diabetic group (p=0.001).

FCS score was higher in the diabetic group than the control group (p=0.02). Since the two groups differed regarding age, education and employment status, a post-hoc ANCOVA test was performed to analyze possible effects of these parameters. Though age was found to affect FCS score (p=0.04), DM and control groups still showed significant difference in FCS scores when age was adjusted (adjusted p=0.01).

There was no significant difference between diabetic and control groups regarding CAS score p=0.37). We also performed a post-hoc ANCOVA test to evaluate differing factors between groups. Post-hoc analysis showed no association between these covariates and CAS scores. CAS scores of 7 patients were nine and above (six patients in the diabetic group and one in the control group). In the diabetic group, pre-pandemic HbA1c, pandemic HbA1c, and disease duration didn't differ between patients with CAS score ≥9 and those with CAS score <9 (p=0.13, p=0.07, and p=0.52, respectively). HbA1c, disease duration, place of residence, employment status, and education status had no effect on FCS and CAS in the diabetic group (all p>0.05). In the diabetic group, anxiety was higher in females than males (p=0.009), however gender showed no effect on FCS (p>0.05).

When the whole population (both diabetic and control groups) is considered, age, place of residence, employment status, and education status showed no association with either FCS or CAS (all p>0.05).

When all patients were evaluated, anxiety was more severe in women (p=0.001), however FCS was not affected by gender (p>0.05).

In the correlation analysis, a positive linear relationship was found between FCS and CAS in the diabetic group (p=0.02, r=0.199). However, HbA1c, diabetes duration, and age had no significant correlation with neither FCS, nor CAS. A positive linear relationship was found between FCS and CAS among all patients (p<0.001, r=0.247).

DISCUSSION

In our study, fear of COVID -19 was higher in diabetic patients than healthy individuals, but the severity of anxiety was similar. There was no relationship between fear and anxiety of COVID-19 and HbA1c. Neither FCS, nor CAS was affected by age, HbA1c, duration of diabetes, place of residence,

Table 1. Comparison of demographic characteristics and test scores of the groups

	Diabetic group (n=168)	Control group (n=81)	p
Age (years)	55 (23-76)	43 (19-76)	<0.001
Gender (female)	120 (71.4%)	66 (81.5%)	0.120
Place of residence			0.253
town/village	136 (81%)	71 (87.7%)	
province/district	32 (19%)	10 (12.3%)	
Employment status			<0.001
employed	40 (23.8%)	40 (49.4%)	
unemployed	128 (76.2)	41 (50.6%)	
Education status			0.003
uneducated/ primary school level	90 (53.6%)	27 (33.3%)	
middle school/upper level	78 (46.4%)	54 (66.7%)	
FCS	19.2 ±7.3	16.9±7,4	0.025
CAS	0 (0-11)	0 (0-17)	0.369

CAS: Coronavirus Anxiety Scale, FCS: The Fear of COVID-19 Scale.

Descriptive data were shown as mean ± SD, median (interquartile range) or number (percentage); p< 0.05 were considered statistically significant

employment status, and education status in the diabetic patients. COVID-19 anxiety was found higher in women, however COVID-19 fear was similar in both genders.

In a large survey study in Danish diabetic patients, an increase in health anxiety such as fear of being infected and inability to manage diabetes during infection was found [2]. In our study, fear of COVID-19 was higher in diabetic patients compared to the general population, but it was found that fear associated with COVID-19 does not affect HbA1c. However, Ahorsu et al. showed a positive relationship between fear of COVID-19 and hospital anxiety and depression [15]. With increased anxiety and depressive symptoms, glucose regulation may be disrupted, and Hb1Ac levels may be impaired [17]. This has been attributed to the deterioration of patients' compliance with treatment in depression. Although the fear of COVID-19 does not affect HbA1c levels, we think that with the long duration of the pandemic, the fear may cause anxiety and depressive state in the future, increasing stress and disrupting glucose regulation.

Ruissen et al. found that anxiety increased during the pandemic in diabetic patients in their study [8]. In our study, the anxiety level was similar between the diabetic and control groups. However, the anxiety level was higher in women compared to men. The literature shows that the COVID-19 pandemic causes more depression and anxiety symptoms, post-traumatic stress disorder, loneliness, and consequently more psychological effects in women [2,18,19]. Women may have culturally expressed their illnesses, complaints, and fears more easily. On the other hand, because the male gender role culturally symbolizes courage and fearlessness, male patients may have avoided seeking help and hid their anxiety until their illness became severe.

In literature, conflicting results were obtained from the studies on HbA1c levels and anxiety during the COVID-19 pandemic. In a study, higher depression and anxiety symptoms were shown in women diabetic patients with HbA1c ≥10% (7). On the other hand, no correlation was found between COVID-19 anxiety and HbA1c in another study [8]. It was also observed that anxiety symptoms did not cause impairment in HbA1c values in diabetic patients, even when there is no pandemic [20]. In our study, we could not find any relationship between HbA1c and COVID-19 anxiety. In addition, it was observed that the HbA1c values of diabetic patients with poor glycemic control improved during the pandemic [8]. This is explained by the fact that people with poor glycemic control emphasize their glycemic control to cope with increased stress levels. The fact that the mortality of COVID-19 infection was higher in patients with impaired blood glucose regulation may also have caused patients to pay more attention to their blood glucose levels.

Our study has some limitations. Short and rapid assessment scales that can be used for screening purposes were used for the pandemic. In addition, the scales used in this study are self-report scales and are evaluated according to the person's statement. The pre-pandemic mental health of patients can affect data. The age, education, and employment status of the people included in the control group were not equated with the diabetic group. The strength of our study is that the patients were interviewed face to face. In addition, it has been shown that short and rapid manner with self-report scales that allow the individual to evaluate themself in non-psychiatric outpatient clinics can be used for screening fear and anxiety. Thus, patients with high fear and anxiety can be referred to an advanced center.

As a result, the fear of COVID-19 is higher in diabetic patients compared to the average population. However, this situation did not have a negative effect on HbA1c values. However, the mental health of diabetic patients may deteriorate with the prolongation of the pandemic period, the fear of getting the infection, the long isolation process, and the high anxiety caused by the quarantine. In the long run, rates of depression may increase. During the COVID-19 pandemic, protecting mental health and increasing psychological resilience are as important as physical health. For this reason, further studies are required to determine and reduce the anxiety and fear caused by the pandemic in diabetic population.

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Author contribution

Study conception and design: ÇTB; data collection: ÇTB and SÖE; analysis and interpretation of results:

ÇTB and SÖE; draft manuscript preparation: ÇTB and SÖE. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Amasya University Ethical Commitee of Non-Invasive Clinical Research (Protocol no: 119 / 12.11.2020).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

The Association Between Comorbidities and a High-Risk Status According to COPD GOLD Groups

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ABSTRACT

Objective: The natural course of the chronic obstructive pulmonary disease (COPD) is thought to be affected by the severity of COPD, frequency of episodes, as well as the presence of comorbid conditions. It was aimed to explore the effect of comorbid conditions on high-risk status in stable COPD patients.

Material and methods: Study participants consisted of stable COPD patients attending to the pulmonology outpatient unit of a tertiary center between 15th May 2018 and 12th Dec 2019. Demographic data, comorbidities, clinical index scores, modified Charlson comorbidity index score (mCCI), BODE index score, and the Short Form 36 (SF-36) scores as a generic life quality measure were recorded. Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups were determined based on symptoms and exacerbations.

Results: There were 23(25.8%), 31(34.8%), 2(2.2%), and 33(37.1%) patients in GOLD gropus A, B, C, and D, respectively. Among these, A and B groups are considered as low-risk, and C and D groups are considered as high-risk. High risk patients had higher mCCI ($p < 0.001$) and were more likely to have hypertension (p=0.012), congestive cardiac failure (p=0.029), chronic renal failure (p=0.022), osteoporosis (p=0.001), and anemia (p<0.001). In a logistic regression analysis performed to examine the determinants of high-risk status in COPD-GOLD groups, biomass exposure was found to increase the likelihood of having a high risk-status by 3-fold.

Conclusion: Classification of stable COPD patients according to GOLD groups showed higher mCCI in subjects with high-risk status. Comorbidities and mCCI did not appear to affect the high-risk status. Biomass exposure was associated with an increased risk of having a high-risk status.

Keywords: chronic obstructive pulmonary disease, global initiative for chronic obstructive lung disease groups, comorbidity, biomass exposure.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable condition that is generally caused by significant exposure to noxious particles or gases and that is characterized by persistant airflow obstruction and respiratory symptoms [1]. Globally, COPD now represents the third common leading cause of death [1]. Although lungs represent the initial site of involvement, COPD is generally considered a complex multi-faceted disorder characterized by chronic systemic inflammation and common occurrence of comorbidities [2,3]. COPD severity, frequency of exacerbations, and presence of comorbidities are known to be associated with symptom severity and worsening of the disease [4,5]. In COPD patients, comorbid conditions have a major impact on the quality of life, frequency of exacerbations, and survival [1,2]. Although the mechanisms have not been defined yet, there are studies indicating that there is a chronic inflammatory condition that accelerates the natural history of some comorbidities in COPD. COPD and other comorbidities are actually considered part of the systemic disease [6,7] .

The objective of this study is to examine the association between comorbidities and GOLD groups among clinically stable COPD patients, and to determine the factors that are more commonly observed among high-risk patients versus low-risk patients. To the best of our knowledge, this is one of the few studies to evaluate the association between comorbidities and GOLD groups in COPD patients.

METHODS

COPD patients who have been admitted between 15th May 2018 and 12th Dec 2019 to the Pulmonology Outpatient Clinics of Hacettepe University, a tertiary care center in Ankara, the capital city of Turkey with a population of around 5.5 million, were investigated for eligibility. Adult patients ≥40 years of age diagnosed with stable COPD according to GOLD 2017 guidelines and who gave consent were included. In order to be eligible, patients had to have a post-bronchodilator FEV1/FVC ratio of < 0.7 (Forced Expiratory Volume at 1 second/ Forced Vital Capacity). In this cross-sectional study, data regarding demographic features, COPD symptoms, and comorbid conditions were collected with a survey. Diagnosis of comorbidities was based on self-report and hospital electronic records. Pulmonary function test results and data that was necessary to calculate the clinical index scores were obtained from hospital electronic records. The body mass index (BMI) was calculated using height and weight of each patient, and was classified according to the World Health Organization (WHO) scheme [8]. The Modified Medical Research Council Dyspnea Scale (mMRC), and the Chronic Obstructive Pulmonary Disease Asssessment Test (CAT) were used to assess the sypmtoms (1). Patients were classified as of GOLD 2017 guideline groups A, B, C, and D COPD.

SF-36

This generic tool for measuring the quality of life includes 8 sections, each containing 2 to 10 items (general health, physical functioning, physical role, emotional role, social functioning, pain, energy, and mental health), each of which is scored in one section only. The score for the scales ranges between 0 and 100, higher scores showing better quality of life [9].

Pulmonary Function Tests

Spirometry tests were carried out according to the European Respiratory Society (ERS) standards, and included FVC and FEV1. Also, the FEV1/FVC ratio was calculated [10,11].

COPD Symptom Assessment Tools

mMRC and CAT were used for symptom assessment. The estimated risk of mortality was calculated using the BODE (Body-mass index, airflow Obstruction, Dyspnea, Exercise) index [1].

Modified Charlson Comorbidity Index

A total of 19 different comorbidities and cancer diagnoses were inquired and scored using the Modified Charlson Comorbidity Index (mCCI). An additional 1-point was added to the current score for each 10 years after age 40, yielding the mCCI score [12,13].

Exercise Performance

In line with the American Thoracic Society (ATS) protocol, the 6-minute walking distance (6-

MWD) was measured. After an initial assessment for potential contraindications using oxygen saturation, pulse, and blood pressure, selected patients underwent the protocol. The severity of dyspnea before and after the procedure was evaluated with modified BORG scale [14].

Ethical Considerations

The study protocol was approved by the Ethics Committee of Hacettepe University for Non-Interventional Clinical Research on 19th Nov 2019 (no. 2019/27-16), and the study was conducted according to ethical principles set forth in Helsinki Declaration. All participants provided written informed consent. No financial support was obtained for the study, and the study authors declared no conflicts of interest. The study results were discussed as an oral presentation at the 25th Annual Congress of the Turkish Thoracic Society that was held between 24th and 28th of May 2022 in Antalya, Turkey [SS-037].

Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation or median (interquartile range) for normally distributed or non-normally distributed continuous variables and as n (frequency percentage) for categorical variables.

Differences between groups were assessed by Student's t-test for normally distributed continuous variables and by Mann–Whitney U test for non-normally distributed continuous variables. Comparisons of categorical variables were carried out by Chi-square test or Fisher's exact test and odds ratio, and its 95% confidence intervals were given as effect size.

A multivariable logistic regression model was built to determine the association between high-risk COPD and modified Charlson Comorbidity Index scores, with adjustment for age, gender, presence of pre-obesity or obesity, current smoking status, and biomass exposure. For the model selection, enter method (based on the likelihood ratio) was used. Model fit was evaluated with the Hosmer-Lemeshow goodness-of-fit test.

All statistical tests were two-tailed, and statistical significance was set at $p<0.05$. All analyses were performed with Statistical Package for the Social Sciences (SPSS) version 23 (IBM, Armonk, NY, USA).

RESULTS

All eligible patients (n=89) provided informed consent and were included in the statistical analyses. Of these 23 (25.8%), 31 (34.8%), 2 (2.2%), and 33 (37.1%) were in GOLD groups A, B, C, and D, respectively. On average, high-risk patients were 8 years older than low-risk patients. Although majority of the patients were male, male predominance was even more marked (87.0%) in the low-risk group.

The patients reported at least one comorbidity were 79.6% in low-risk group and 91.4% in high-risk group (p=0.15). The mean mCCI scores (± SD) in high-risk and low-risk patients were significantly different (6.7 ± 2.72 versus 4.7 ± 2.56, respectively; $p < 0.001$). Similarly the median number [IQR] of comorbidities showed a significant difference between low-risk and high-risk patients (2.0 [3.0] versus. 5.0 [5.0]; p=0.001). There was no statistically significant difference between high and low risk patients in terms of presence of diabetes mellitus (p=0.86), obstructive sleep apnea syndrome (p=0.076), bronchiectasis (p=0.22), and malignancy (p=0.90). Hypertension (p=0.012), congestive heart disease (p=0.029), chronic renal failure (p=0.022), osteoporosis (p=0.001) and anemia ($p<0.001$) were more common in the high-risk group than in the low-risk group, and the difference was statistically significant (Table 1).

Biomass exposure was significantly higher among high-risk patients (62.9%) as compared to low risk (37.0%) patients. Table 1 shows the demographic characteristics, comorbidities, disease burden, clinical parameters, and scores according to GOLD groups.

Table 2 shows SF-36 results according to GOLD groups. In all 8 sections of SF-36, high-risk patients had significantly lower quality of life scores as compared to low-risk patients.

The treatments received by the patients included long-acting beta-agonist (LABA) and long-acting muscarinic antagonist (LAMA) and LABA + ICS combined preparations, short acting inhaler, and systemic theophylline. No patients received systemic steroids or roflumilast. Table 3 shows the distribution of treatments according to GOLD groups.

Age, gender, BMI were included as potential confounders, and current smoking (a proven risk

factor for high-risk COPD) and biomass exposure were included as covariants in a logistic regression model built to assess the relationship between mCCI scores and high-risk COPD status. Model fit was evaluated with the Hosmer-Lemeshow goodness-of-fit test (p=0.79). Nagelkerke's R2 of the model was 0.300. Subsequently, the modified CCI score lost its significance in the model. Biomass exposure 3.08 times increased the status of being in the high-risk GOLD group (95% CI = 1.10-8.62; p=0.033) (Table 4).

Table 1. Demographic characteristics, comorbid conditions, and disease severity according to COPD GOLD groups

Variable	Overall (n= 89)	High Risk Groups C and D (n= 35)	Low Risk Groups A and B (n= 54)	OR (95% CI)	P-value
Demographics					
Age, y	66.3 ± 10.58	71.0 ± 9.60	63.2 ± 10.12	-	**<0.001**
Male	70 (78.7)	23 (65.7)	47 (87.0)	0.29 (0.01-0.82)	**0.016**
BMI, kg/m^2	27.1 ± 5.84	26.4 ± 6.45	27.5 ± 5.42	-	0.38
Current smoker	78 (87.6)	26 (74.3)	52 (96.3)	0.11 (0.02-0.55)	**0.006***
Biomass exposure	42 (47.2)	22 (62.9)	20 (37.0)	2.88 (1.19-6.94)	**0.017**
Long-term oxygen therapy	27 (30.3)	20 (57.1)	7 (13.0)	8.95 (3.17-25.29)	**<0.001**
Use of nebulizer	27 (30.3)	19 (54.3)	8 (14.8)	6.83 (2.50-18.62)	**<0.001**
Non-invasive mechanical ventilation	11 (12.4)	6 (17.1)	5 (9.3)	2.03 (0.57-7.24)	0.33
Allergy	10 (11.2)	4 (11.4)	6 (11.1)	1.03 (0.27-3.96)	1.00*
Comorbidities	75 (84.3)	32 (91.4)	43 (79.6)	2.73 (0.70-10.59)	0.15
Diabetes mellitus	22 (24.7)	9 (25.7)	13 (24.1)	1.09 (0.41-2.91)	0.86
Hypertension	49 (55.1)	25 (71.4)	24 (44.4)	3.13 (1.26-7.75)	**0.012**
Obstructive sleep apnea syndrome	5 (5.6)	-	5 (9.3)	-	0.076*
Congestive heart failure	22 (24.7)	13 (37.1)	9 (16.7)	2.96 (1.10-7.96)	**0.029**
Chronic renal failure	11 (12.4)	8 (22.9)	3 (5.6)	5.04 (1.23-20.56)	**0.022***
Bronchiectasis	11 (12.4)	6 (17.1)	5 (9.3)	2.03 (0.57-7.24)	0.22*
Malignancy	17 (19.3)	7 (20.0)	10 (18.9)	1.08 (0.37-3.16)	0.90
Osteoporosis	26 (29.2)	17 (48.6)	9 (16.7)	4.72 (1.78-12.53)	**0.001**
Anemia	44 (49.4)	27 (77.1)	17 (31.5)	7.35 (2.77-19.49)	**<0.001**
Charlson comorbidity index score	5.45 ± 2.79	6.7 ± 2.72	4.7 ± 2.56	-	**<0.001**
COPD severity					
BODE Index	3.0 [5.0]	8.0 [4.0]	2.0 [2.0]	-	**<0.001**
0-2 (reference)	34 (38.2)	2 (5.7)	32 (59.3)	1.00	**<0.001**
3-4	17 (19.1)	2 (5.7)	15 (27.8)	2.13 (0.28-16.63)	
5-6	13 (14.6)	9 (25.7)	4 (7.4)	36.0 (5.65-229.3)	
7-10	25 (28.1)	22 (62.9)	3 (5.6)	117.3 (18.09-761)	
GOLD stage					**0.006***
I. (reference)	10 (13.9)	5 (22.7)	5 (10.0)	1.00	
II.	34 (47.2)	4 (18.2)	30 (60.0)	0.13 (0.03-0.67)	
III.	22 (30.6)	10 (45.5)	12 (24.0)	0.83 (0.19-3.72)	
IV.	6 (8.3)	3 (13.6)	3 (6.0)	1.00 (0.13-7.57)	
CAT score	17.5 ± 10.45	25.8 ± 9.35	12.2 ± 7.13	-	**<0.001**
mMRC score	2.0 [3.0]	4.0 [1.0]	1.5 [1.0]	-	**<0.001**
6MWT distance, m	390.0 [381.0]	50.0 [100.0]	480.0 [183.0]	-	**<0.001**

Values are presented as mean ± standard deviation, median [interquartile range] or number (%).

6MWT = 6-minute walk test; GOLD=Global Initiative for Chronic Obstructive Lung Disease;

CAT=COPD Assessment Test; mMRC= Modified Medical Research Council Dyspnea Scale; BMI= Body Mass Index;

OR= Odds ratio, CI = Confidence interval

* Fischer's exact test p-value

Table 2. Distribution of quality of health short form-36 in COPD GOLD groups

Short form-36	Overall (n=89)	High Risk Groups C and D (n=35) Mean ± SD Median [IQR]	Low Risk Groups A and B (n=54) Mean ± SD Median [IQR]	p-value
Physical functioning	65.0 [75.0]	10.0 [30.0]	77.5 [31.0]	**<0.001**
Role limitations due to physical health	0.0 [50.0]	0.0 [0.0]	50.0 [81.0]	**<0.001**
Role limitations due to emotional problems	100.0 [100.0]	0.0 [100.0]	100.0 [75.0]	**<0.001**
Energy/fatigue	50.0 [30.0]	40.0 [35.0]	60.0 [31.0]	**<0.001**
Emotional well-being	64.0 [22.0]	60.0 [36.0]	66.0 [22.0]	**0.014**
Social functioning	62.5 [75.0]	25.0 [25.0]	87.5 [37.5]	**<0.001**
Pain	100.0 [22.5]	100.0 [55.0]	100.0 [152.5]	**0.001**
General health	49.9 ± 20.46	37.9 ± 16.06	57.7 ± 19.30	**<0.001***

SD: Standard deviation, IQR: Interquartile range

*Student's t-test

Table 3. Distribution of treatment in COPD-GOLD groups

Treatment	Overall patient (n=89) n (%)	Groups C and D (n=35) n (%)	Groups A and B (n=54) n (%)	OR (95% CI)	p-value
Inhalers					
Any short-acting	27 (30.3)	17 (48.6)	10 (18.5)	4.16 (1.60-10.79)	**0.003**
LABA only	5 (5.6)	-	5 (9.3)	-	0.076*
LAMA only	36 (40.4)	16 (45.7)	20 (37.0)	1.43 (0.60-3.40)	0.42
LABA+LAMA	7 (7.9)	1 (7.9)	6 (11.1)	0.24 (0.03-2.05)	0.16*
LABA+ICS	45 (50.6)	19 (54.3)	26 (48.1)	1.28 (0.55-3.00)	0.57
Systemic medications					
Theophylline	4 (4.5)	3 (8.6)	1 (1.9)	4.97 (0.50-49.8)	0.17*

OR = Odds ratio, CI = confidence interval, LABA = Long-acting beta 2 agonist, LAMA = Long-acting muscarinic antagonist, ICS = inhaled corticosteroids

* Fischer's exact test p-value

Table 4. Results of a logistic regression analysis for determinants of high-risk status according to COPD-GOLD groups

	Univariate			Multivariate		
	crude OR	95% CI	p-value	adj OR	95% CI	p-value
Charlson Comorbidity Index score	1.33	1.12 – 1.59	0.001	1.13	0.88 – 1.43	0.34
Male gender	0.29	0.10 – 0.82	0.020	0.53	0.13 – 2.23	0.39
Age (years)	1.08	1.03 – 1.14	0.001	1.05	0.98 – 1.12	0.18
Pre-obesity and obesity (BMI >25kg/m^2)	0.81	0.34 – 1.96	0.65	0.62	0.22 – 1.76	0.37
Biomass exposure	2.87	1.19 – 6.94	0.019	3.08	1.10 – 8.62	0.033
Current smoking	0.11	0.02 – 0.55	0.007	0.55	0.08 – 4.00	0.56

OR: odds ratio, adj: adjusted, CI: confidence interval, BMI: Body-mass index

DISCUSSION

As a result of this cross-sectional study, there was no association between high-risk GOLD group and the presence of at least one comorbidity, while the number of modified CCI and reported comorbidities was higher in high-risk GOLD group. No association was found between high-risk COPD and diabetes mellitus, obstructive sleep apnea syndrome, bronchiectasis, and malignancy, while hypertension, congestive heart disease, chronic renal failure, osteoporosis, and anemia were more common in the high-risk group than in the low-risk group.

The most likely reason for the absence of a statistically significant association between the presence of at least one comorbidity and high-risk GOLD group was the high prevalence of at least one comorbid condition in all COPD patients, regardless

of risk status. Although there was no statistically-significant association, it was also found that at least one comorbid condition was more common in the high-risk group.

Modified CCI is valuable as it is a standardized indicator in the evaluation of comorbid condition. The mean mCCI was 2 points higher in the high-risk group than in the low-risk group. Similarly, the median number of comorbidities between high- and low-risk GOLD groups was 5 and 2, respectively.

However, the statistical significance of the mCCI score was lost in the multivariate analysis, probably due to the fact that this scoring system is mainly used to predict mortality and also due to the fact that the effect of age was eliminated when adjustments for age was performed, although increased age was associated both with high-risk GOLD group and higher mCCI scores. The association between mCCI and high-risk GOLD group persisted when age was excluded from the model (OR=1.24; 95%CI=1.02 – 1.51; p=0.030). High-risk patients also had higher number of comorbidities. In a 2021 study, a mCCI score of ≥ 3 were found to be potential causes of low FEV1 in COPD patients followed-up for 1 year [15]. Also, in a study from 2018, arrhtyhmia, osteoporosis and certain other comorbidities were significantly more common in patients with GOLD groups C and D [16]. In a study conducted in the UK, in which 2620 patients who were classified as mild, moderate and severe for airway obstruction level according to the COPD-GOLD criteria, were evaluated. Especially in cardiovascular diseases (hypertension, coronary artery disease, diabetes, stroke/TIA, AF, HF) there is an increasing trend from mild to severe airway obstruction [17]. In a study conducted in Moldova between 2015 and 2017 in 435 patients, heart failure was determined with increasing frequency in 2011 COPD-GOLD B, C and D groups, but no significant difference was found in terms of hypertension and coronary heart disease [18].

Among our participants, smoking was more common in those with low-risk status. Firstly, this was a cross-sectional study providing no reliable information on past history of smoking, and this apparent paradox could be related with the fact that increasing disease burden could have led to increased quitting. In another prospective study from our country involving 463 COPD patients, current smoking was found to be less common in GOLD group C and D patients, as compared to those in GOLD groups A and B, similar to our findings [19]. In a 2017 study by Sun et al. classifying patients according to GOLD 2017 guidelines, the current smoking rate was also shown to decreasing trend among GOLD groups A to D. [20].

Low or high risk COPD patients according to GOLD classification did not differ significantly in terms of body mass index. Similarly, a previous study reported comparable BMI values across GOLD A, B, C, and D group patients [20]. A logistic regression analysis showed that obesity was associated with a 1.6 increased likelihood of having a low-risk status. Cachexia and underweight are associated with a worse prognosis and increased mortality in patients with severe COPD [21]. Obese patients were more likely to be in the low-risk group. It has been reported that obesity is not associated with a worsening of pulmonary functions and may have a protective effect against mortality [22]. A significantly increased risk of COPD was reported in underweight individuals versus overweight individuals [23]. Metabolic syndrome and abdominal obesity are more common in mild to moderately severe COPD patients in comparison with severe COPD patients [24].

In this study, the high-risk COPD patients were found to have higher biomass exposure than low-risk patients (p=0.017). According to a multi-variate analysis, exposure to biomass exposure was associated with a 3.08-fold increased likelihood of having a high-risk COPD status. Biomass exposure is known to be particularly higher in developing countries and in rural areas [25]. In the developing world, approximately 50% of the COPD related deaths result from biomass exposure. Similarly, women with indoor exposure to smoke have been reported to be 3-times more likely to develop COPD as compared to women who cook using cleaner heat sources such as electricity and gas [26,27]. For example, in a study from Columbia, the use of biomass stoves for ≥ 10 years was associated with higher risk of COPD [26]. In another study, biomass exposure was found to be associated with reduced quality of life in COPD patients. Camp et al., observed more severe symptoms and worse clinical scores in female COPD patients with biomass exposure than in female smoker COPD patients [28]. In another study including 138 female patients with COPD and similar obstruction, reduced quality of life and

worse clinical scores were found among those with biomass exposure [26].

Increasing disease severity in the participants of this study was associated with reduced life quality scores. Also, severe COPD patients had lower quality of life scores than mild to moderately severe cases. Patients with GOLD group A and B disease were reported to have better life quality indices than in the other groups. This was explained on the basis of social isolation due to reduced mobility, which was caused by more severe disease in GOLD C and D groups [29].

Due to the cross-sectional design of our study, it is not possible to determine cause and effect relationships. Also, since it only included patients attending to an outpatient unit, the results may not be generalizable to the general population. Other factors that limit the generalizability of our observations include the single-center design and lack of random sampling. However, the internal reliability of our results may be high, as the missing data was minimal, and objective methods were used for patient assessment in addition to patients' self-reports. In any case, the recall factor should be taken into consideration for data collected on the basis of patients' reports.

In conclusion, to the best of our knowledge, this is the first study in our country investigating the association between comorbidities and COPD GOLD groups. While no associations were found between comorbidities and high-risk status, biomass exposure emerged as a significant risk factor. To better elucidate the potential associations between comorbidity and high-risk COPD status, further multi-center studies with samples more representative of the general population are warranted. Such studies may also shed more light on the dose-response relationship for biomass exposure in representative patient populations.

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Author contribution

Study conception and design: ÜÖS, ED, LÇ; data collection: ÜÖS, KH, AÖ; analysis and interpretation of the results: ÜÖS, AS, KH, AÖ, ED, LÇ; draft manuscript preparation: ÜÖS, AS. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ethics Committe of Hacettepe University for Non-Interventional Clinical Research (Protocol no. 2019/27-16 / 19.11.2019).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Perceptions of Work and Educational Environment as Predictors of Burnout Among Residents During COVID-19 Pandemic

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ABSTRACT

Objective: Burnout negatively affects personal well-being by reducing job-related satisfaction besides deeply affecting physician lives outside the working environment. This study aimed to determine residents' burnout levels and related psychosocial risk factors regarding the work and educational environment during the COVID-19 pandemic at a university hospital.

Material and Method: Data were collected using an online questionnaire consisting of questions screening the participants' sociodemographic, clinical and, educational characteristics and the following scales; Postgraduate Hospital Educational Environment Measure (PHEEM), Maslach Burnout Inventory (MBI), Rosenberg Self Esteem Scale (RSES).

Results: Of the 632 residents receiving postgraduate education in clinical fields at the university, 99 (15.7%) participated in study, 77 (77.8%) of which reported that they were from medical branches and 12 (12.1%) from surgical branches.The emotional exhaustion (EE) dimension of burnout emerged as the most strongly related dimension with perceptions of the educational environment (PHEEM) (p<0,001, r=-0,548). The depersonalization (DP) dimension was only moderately associated with the perception of low role autonomy (p=0,006, r=-0,273). The low personal achievement (LPA) dimension of burnout, on the other hand, showed a moderate-high correlation with all the components related to the educational environment and showed the most substantial relationship with the perception of low social support (p<0,001, r=-0,372). Decrease in the organizational commitment with the departments and institutions where residents received training and worked was associated with higher levels of burnout and low self-esteem. 30.7% of the participants perceive their health as moderate/poor, and scored higher in all dimensions of burnout (EE p<0,001, DP p=0,001, LPA p=0,001).

Conclusion: In this study, we found that residents' perceptions about the educational environment are the variables most closely related to their burnout levels. With precautions, residents may be protected from burnout-related physical and mental diseases while academic efficiency increases and the healthcare service become more qualified.

Keywords: burnout, residency, COVID-19.

INTRODUCTION

The concept of burnout was first defined as physical and emotional exhaustion caused by weariness, failure, loss of power and energy, unmet demands [1]. Maslach interpreted burnout as a syndrome consisting of three dimensions: emotional exhaustion, depersonalisation, and low personal achievement [2]. When individuals cannot cope with the excessive demand in the workplace, they become insensitive to the people they serve. If this happens, they feel a mismatch between the contribution they expect to make to society or the institutions they work for and their current behaviors. As a result, they conclude that their achievements are insufficient [3].

Studies around the world have shown that approximately one-third to half of the physicians experience at least one dimension of burnout [4-6]. Burnout negatively affects personal well-being by reducing job-related satisfaction [7,8] besides deeply affecting physicians' lives outside the working environment [9]. When the effects of burnout in physicians on health are evaluated, it has been shown that it is associated with an increase in the risk of cardiovascular disease, short life expectancy, uncontrolled alcohol use, unhealthy interpersonal relationships, depression, and suicide [10,11]. Inevitably, burnout in physicians will directly or indirectly reflect on patients. Burnout, which results in deterioration in the mental and physical health of the physician, causes an increase in medical errors, late diagnosis, a decrease in the quality of patient care, and an increase in morbidity and mortality [10,12]. The World Health Organization (WHO) and the US National Institute of Medicine define the quality of health care in six dimensions: effectiveness, efficiency, safety, patient-centered care, accessibility, equity [13,14]. It is thought that physicians' burnout affects all six dimensions negatively [15].

Burnout is quite common among residents, one of the most critical service delivery stakeholders in health institutions where postgraduate education is provided [16,17]. Among the various factors that increase the risk of burnout in the workplace, the most common ones are high expectations regarding the health care service and academic obligations, long working hours, lack of autonomy, inconsistencies between home and work life, the perception of lack of reciprocity in professional relationships, and uncertainties about the future [18-21].

Regarding residents, the place defined as the workplace is also a learning environment where education and research are carried out together with health service delivery to gain postgraduate competencies. It has been suggested in the literature that adversities in the learning environment such as ones regarding characteristics of educators (teaching styles, levels of feedback, and support), residents' feelings of inadequacy, a vague sense of autonomy, the uncertainty of roles and responsibilities, harassment/intimidation problems, lack of education-service balance, negative relationships with peers, and wrong career choice contribute to burnout of the residents [22].

The unfavorable characteristics of the psychosocial aspects of the work and educational environment also contribute to burnout by causing low self-esteem, making the person feel unsuccessful in the workplace and interpersonal relations, and causing insufficient development of the physician identity [23]. This leads to many problems which have reflections on the individual and health care, including physical fatigue, mental depression, negative physician-patient relationships, and increased incidence of medical errors [16,22].

The pandemic process that we have been in since March 2020 has led to many changes and related problems that create physical and mental strain in the working and educational environment of residents and pose a risk of burnout [24] and related psychosocial problems [25]. Psychosocial problems arising from changes can increase the risk of burnout and adversely affect the physical and mental health of residents who are continuing postgraduate education besides providing health services under challenging conditions caused by the pandemic.

Determining the factors that cause burnout and impairment in residents' physical and mental health during the pandemic periods may guide the interventions to prevent burnout at the institutional level.

This study aimed to determine residents' burnout levels and related psychosocial risk factors regarding the work and educational environment during the

Covid-19 pandemic at Hacettepe University Faculty of Medicine.

MATERIALS AND METHODS

Sample and Data Collection

The participants of this descriptive study are residents continuing their postgraduate medical training in a clinical field (medicine or surgery) at Hacettepe University Faculty of Medicine. The information about the research, the invitation text, and the survey link was sent to the e-mail addresses of the residents. Data is collected with the electronic data collection method (Google Forms) between 14.10.2020 and 28.01.2021.

Measures

Data were collected using an online battery of study measures via Google forms consisting of questions screening the participants' sociodemographic, educational characteristics, related opinions and the following scales.

Postgraduate Hospital Educational Environment Measure (PHEEM): The scale was developed [26] for the evaluation of the postgraduate clinical education environment. The Cronbach's alpha reliability coefficient of the original form of the scale was 0.91, while that of the Turkish version was 0.94 [27]. The scale consists of 3 dimensions, including the perception of role autonomy, teaching, and social support, and a total of 40 items that are scored on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree). To interpret the scores, the following scoring intervals are recommended: "very poor" = 0–40, "plenty of problems," = 41–80, "more positive than negative, but room for improvement" = 81–120, and "excellent" = 121–160. While the scores obtained from the role autonomy sub-dimension are evaluated from very poor to excellent; teaching subdimensions are evaluated as inferior quality to model teachers; social support sub-dimension can be interpreted from nonexistent to good a good supportive environment.

Maslach Burnout Inventory (MBI): The scale is developed especially for occupational fields that require face-to-face contact and aim to serve people directly [2] and defined by three subscales representing three dimensions of burnout: emotional exhaustion (EE), depersonalization (DP) and low personal accomplishment (PA). As the 7-point Likert-type response method in the original form of the scale was not found to be applicable for Turkish population in the adaptation study of the scale into Turkish, the study was conducted with a 5-point Likert-type version [28]. EE dimension (9 items, 0-36 points) refers to a decrease in the emotional and physical resources of the individual. DP dimension (5 items, 0-20 points) represents the interpersonal dimension of burnout and expressing negative, rigid attitudes towards the people served and unresponsiveness to work. The low professional accomplishment dimension (8 items,0-32 points) expresses the tendency of the person to evaluate himself negatively. Due to the different answering methods, the scores obtained from the subscales cannot be compared with the scores obtained due to the studies in which the original scale was used. In this study, the personal achievement subscale was scored in the opposite direction, and the expression 'low personal achievement' was used to facilitate analysis and interpretation. The increase in the scores obtained from the subscales corresponds to the increasing level of burnout. No "cut-off point" was used for the dimension scores since cut-off points have not been determined for Turkish population [29]. Although the subscales are related, they measure different concepts. Therefore, it is not possible to obtain a total burnout score and burnout level should be evaluated and interpreted separately for each dimension.

Rosenberg Self Esteem Scale (RSES): The ten-item subscale of the Likert-type scale (30) was used. The Cronbach alpha reliability coefficient of the Turkish version was 0.71 (31). A high score on the scale indicates low self-esteem. A score of 0-6 can be obtained from the scale, and those who score 0-1 are considered to have "high"; those who score 2-4 have "medium," and those who score 5-6 have "low" self-esteem.

Analysis of data

SPSS 23.0 package program was used to evaluate the data. All the data were evaluated in terms of a normal distribution by Kolmogorov-Smirnov, then, statistical tests were determined accordingly. Student t-test, Mann Whitney U test, ANOVA (Tukey post hoc test) and Kruskal Wallis tests are used. We approved significance levels as $p<0.05$, and did Bonferroni correction after ANOVA and Kruskal Wallis tests.

RESULTS

Of the 632 residents receiving postgraduate education in clinical fields at the university, 99 (15.7%) participated in study, 77 (77.8%) of which reported that they were from medical branches and 12 (12.1%) from surgical branches.

The sociodemographic characteristics of the residents participating in the study are shown in Table 1. The mean duration of residency is 25.8 (±15.6, IQR:24) months; the rate for 1 year or less, 1-3 years, and more than 3 years was 28%, 47.9%, was 24%, respectively. 56.8% of the residents stated that the reason for choosing the specialty was that it was their interest.

Residents' perceiving their health, having a disease diagnosed by the physician, applying to the physician for any physical/mental complaints in the last 3 months, finding the application process to the physician similar to the pandemic period is shown in Table 1. All but one of the 25 participants (25.3%) who stated that they had a current psychiatric disorder, reported being diagnosed before the pandemic. Ten residents reported that they continued psychiatric treatment during the pandemic period.

Table 2 shows the distribution of residents according to their Perceptions of Postgraduate Hospital Education Environment. Table 3 shows Postgraduate Hospital Educational Environment; Maslach Burnout Inventory, Rosenberg Self Esteem Scale results. PHEEM scale total score averages of those with a residency period of 1 year or less are statistically higher than those with residency training for 1-3 years and more than 3 years (1 year or less: 100.37 ±28.54; 1-3 years:79.4 ±24.49; > 3 years: 73.78 ± 29.42, p=0.001. Data not shown in the table).

The scores of the residents participating in the study on the PHEEM scale did not differ according to gender (p= 0.721), age group (p= 0.134) and an emotional relationship (p=0.871). MBI EE subscale score was not differed according to gender, age group, and being in an emotional relationship (having a partner) (respectively; p=0,812; p=0,811; p= 0,746); DP subscale score was not differed by gender, age group, and emotional relationship (respectively; p=0.681; p=0.715; p= 0.210). While the LPA subscale score did not differ according to

Table 1. Sociodemographic characteristics, physical and mental health, and treatment-seeking characteristics of the participants

Characteristics (n=99)	n (%)
Gender	
Female	61 (60.4)
Male	35 (35.4)
Doesn't want to specify	3 (3.0)
Age	
25-29 years	70 (70.7)
30 years and older	29 (29.3)
Marital status	
Married, lives with spouse	34 (34.3)
Single	63 (63.6)
Married, lives apart from spouse	1 (1.0)
Divorced	1 (1.0)
Child	
No	90 (89.1)
Yes	9 (8.9)
Perception of economic situation	
Bad	10 (9.9)
Middle	51(51.5)
Good	37 (37.4)
Very good	1(1.0)
People living together	
Parents	16 (15.8)
Friends	8 (7.9)
Spouse/children	34 (34.3)
Alone	32 (32.3)
Responsibility to care/ care liability/duty of care	
Yes	18 (17.8)
No	81(81.8)
Tobacco use	
No	69 (69.7)
Regularly	15 (14.9)
Sometimes	10 (10.1)
Quit	5 (5.0)
Alcohol consumption regularly	
No	41 (41.4)
Yes	12 (11.9
Sometimes	45 (45.5)
Quit	1 (1.0)
Perceived health	
Excellent	9 (8.9)
Good	59 (59.6)
Moderate	30 (29.7)
Bad	1 (1.0)
Diagnosed disease	
No	75 (75.8)
Yes, s/he is on medication	24 (23.8)
Consulting a physician for any physical/mental complaint in the last three months	
No	72 (72.7)
Yes	27 (26.7)
The similarity of the possibilities regarding the application and treatment process with the pre-pandemic period (n=27)	
Yes, similar	12 (44.4)
No, more difficult than pre-pandemic period	14 (51.9)
No, easier than pre-pandemic period	1 (3.7)

Table 2. Residents' perceptions about postgraduate hospital education environment

(n=99)	n (%)
Perceptions of role autonomy	
Very poor	5 (5.0)
A negative view of one's role	42 (42.4)
A more positive perception of one's job	37 (37.4)
Excellent perception of one's job	15 (14.9)
Perceptions of teaching	
Very poor quality	9 (8.9)
In need of some retraining	38 (38.4)
Moving in the right direction	36 (36.4)
Model teachers	16 (15.8)
Perceptions of social support	
Non-existent	7 (6.9)
Not a pleasant place	46 (46.5)
More pros than cons	35 (35.4)
A good supportive environment	11 (10.9)
PHEEM totally	
Very poor	5 (5.0)
Plenty of problems	39 (39.4)
More positive than negative but room for improvement	43 (43.4)
Excellent	12 (11.9)

Abbreviations: PHEEM, Postgraduate Hospital Educational Environment Measure

Table 3. Participants' PHEEM, MBI and RSES

Scores (Min-Max)	Mean	SD
PHEEM		
Perceptions of role autonomy (0-53)	30,0	10,4
Perceptions of teaching (2-58)	32,6	12,1
Perceptions of social support (0-40)	22,4	7,7
Totally (2-147)	**84,9**	**28,8**
MBI		
Emotional exhaustion (1-34)	19,3	7,5
Depersonalization (1-18)	9,0	4,1
Low personal acomplishment (3-28)	13,6	4,7
RSES (0-4,84)	1,5	1,0

Abbreviations: PHEEM, Postgraduate Hospital Educational Environment Measure; MBI, Maslach Burnout Inventory; RSES, 27 Self Esteem Scale

age group and emotional relationship (respectively; p=0.930; p=0.525), women scored higher on this subscale than men (14.4/12.0) (p=0.016). There was no relationship between the duration of residency and levels of burnout and self esteem (emotional exhaustion p=0.151, depersonalization p=0.756, low personal achievement p=0.531, RSES p=0.930). The scores obtained from the RSES did not differ according to gender, age group, and emotional relationship (respectively; p=0.137; p=0.912; p= 0.122).

Participants who stated that they had been treated for a psychiatric illness in the past had similar scores on all three subscales of the MBI and RSES (EE: p= 0.575; DP: p= 0.550; LPA: p = 0.965; RSES: p=0.304). Emotional burnout scores of those who have received psychiatric treatment in the past and those currently on treatment are higher than those who are not on treatment. ((24,1 ±7,3/17,4 ±5,5), p =0,026).

30.7% of the participants perceive their health as moderate/poor (Table 1), and showed higher

burnout in all sub-dimensions. Participants who perceive their health as moderate/poor scored higher in all dimensions of burnout compared with those who perceive their health as good/very good (p<0.001, p=0.002, p=0.001 respectively, Table 4). Table 4 shows the relationship of residents' burnout levels and self-esteem scores with perceptions of education and work environment characteristics and their health. Residents who had applied to a physician with any physical and mental complaints in the last 3 months were compared with those who did not apply for any complaint. The scores of both groups on EE (p=0.345), DP (p=0.749), LPA (p=0841), and RBSS (p=0.116) were found to be similar. The rate of those who are satisfied with being a resident was 38.4%; moderately satisfied was 34.3%; dissatisfied was 27.3%. 10.1% of the residents stated that they thought of quitting residency frequently; 57.6% occasionally; 32.1% never thought of quitting. 73.7% of the participants stated that they had to give up their interests/hobbies during the residency process, the reasons why they gave up is 82.2% could not find enough time; 16.4% did not have physical energy; 1.4% reported that were no longer interested and enjoy it. When the views on the physical conditions of the working and educational environments are examined, the rate of those who are not satisfied was 39.3%; moderately satisfied was 31.3%; dissatisfied was 39.3%.

The PHEEM total score and subscale score averages of the participants who felt organizational commitment and those who did not, differed in terms of both the total score and the subscale scores (Table 5). The findings of the correlation analysis of the PHEEM, MBI Subscales, and RSES are shown in Table 6.

DISCUSSION

In this study we aimed to determine residents' burnout levels and related psychosocial risk factors regarding the work and educational environment during the Covid-19 pandemic at a university hospital and found that that residents' perceptions about the educational environment were found to be the variables that are most closely related to

Table 4. The relationship of residents' MBI, EE, DP, PA, RSES with perceptions of education and work environment and perceptions of health

	EE		DP		PA		RSES	
	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p
If you had the chance to choose again, would you choose the same department?								
Yes (n=50)	15,6 (6,8)*	<0,001	8,1(4,3)	0,014 †	11,7(4,2)*	<0,001	1,1 (0,8)*	0,001
No (n=26)	24,6 (5,9)		11,0(3,3)		16,0(4,3)		1,9(1,1)	
Undecided (n=23)	21,6 (6,5)		8,5 (3,9)		14,9(4,5)		1,9(1,0)	
If you had the chance to choose again, would you choose the institution?								
Yes (n=35)	15,9 (7,2)*	<0,001	7,8(4,1)*	0,003	12,1(4,1)*	0,053	1,0(0,2)	0,034
No (n=31)	23,5 (6,1)		11,0(3,4)		15,3(5,2)		1,7(0,9)	
Undecided (n=33)	19,1 (7,4)		8,3(4,2)		13,5(4,4)		1,6(0,9)	
What is the education-service balance of your department?								
The education is more important. (n=18)	14,8 (6,5) ‡	0,001	8,2(4,5)	0,066	12,7(4,2)	0,138	1,1(0,9)	0,112
The service is more important. (n=53)	21,8(6,7)		9,9(3,9)		14,5(5,0)		1,6(0,9)	
Balanced (n=28)	17,8(8,1)		7,8(4,2)		12,6(4,2)		1,5(1,1)	
Do you feel organizational commitment to your institution?								
Yes (n=57)	18,0(7,9)	0,075	8,8(4,3)	0,549	12,9(3,9)	0,261	1,5(1,1)	0,293
No (n=42)	21,9(6,7)		9,4(4,2)		14,8(5,9)		1,7(0,8)	
What do you think is the level of your own health?								
Excellent/Good	17,4 (7,3)	<0,001	8,1(4,2)	0,002	12,6 (4,8)	0,001	1,5 (0,9)	0,350
Moderate/Bad	23,6 (6,3)		10,0 (3,4)		15,7 (3,8)		1,7 (1,1)	

Scores compared using ANOVA, Kruskall Wallis, Tukey, Student t test, Mann Whitmey U

*The difference is due to the "Yes" group, † The difference is between the Yes-No group, ‡ The group from which the difference originate

Abbreviations: MBI, Maslach Burnout Inventory; EE, Emotional exhaustion; DP, Depersonalisation; PA, Low personal achievement; RSES, Rosenberg Self Esteem Scale; SD, standard deviation

Table 5. PHEEM scores according to feeling organizational commitment of participants

	Feeling organizational commitment		p
	Yes	No	
	Mean (sd)	Mean (sd)	
PHEEM			
Perceptions of role autonomy	33,3 (9,7)	24,4 (10,2)	<0,001
Perceptions of teaching	36,6 (11,3)	26,1 (11,3)	<0,001
Perceptions of social support	25,4 (7,2)	18,4 (6,9)	<0,001
Totally	95,2 (26,9)	69,0 (26,6)	<0,001

Abbreviations: PHEEM, Postgraduate Hospital Educational Environment Measure

Table 6. Correlation analysis of the PHEEM, MBI subscales scores and RSES

	EE, P (rs)	DP, P (rs)	PA, P (rs)	RSES, P (rs)
PHEEM				
Perceptions of role autonomy	<0,001 (-0,585)	0,006 (-0,273)	<0,001 (-0,317)	0,031 (-0,217)
Perceptions of teaching	<0,001 (-0,879)	0,092 (-0,170)	<0,001 (-0,340)	0,010 (-0,258)
Perceptions of social support	<0,001 (-0,512)	0,039 (-0,207)	<0,001 (-0,372)	0,002 (-0,305)
Totally	<0,001 (-0,548)	0,024 (-0,227)	<0,001 (-0,356)	0,008 (-0,265)
Maslach Burnout Inventory				
Emotional exhaustion (EE)				<0,001 (0,357)
Depersonalization (DP)				0,004 (0,287)
Low personal acomplishment (PA)				0,030 (0,218)

Abbreviations: PHEEM, Postgraduate Hospital Educational Environment Measure; MBI, Maslach Burnout Inventory; EE, Emotional exhaustion; DP, Depersonalisation; PA, Low personal achievement; RSES, Rosenberg Self Esteem Scale; SD, standard deviation; rs, Pearson or Spearman correlation coefficient

their burnout levels. Decrease in the organizational commitment with the departments and institutions where residents received training and worked was associated with higher levels of burnout and low self-esteem. Another important finding of the study is that perception of health was closely related to all dimensions of burnout. These results indicates that, with precautions, residents may be protected from burnout-related physical and mental diseases while academic efficiency increases and the healthcare service become more qualified.

In a study conducted in Saudi Arabia, most residents stated a decrease in educational activities during the pandemic; most emphasized the decline in surgical practice and indicated that they did not feel psychologically ready even though they had time to study. It was stressed that junior residents felt more insecure and vulnerable [32]. A study conducted with obstetrics residents in Italy emphasized that education came to a standstill during the pandemic. Most of the residents stated that their education was irreversibly interrupted. 84% of the residents indicated that they were worried about the future; there was no significant relationship between seniority and the level of anxiety [33]. In a study conducted in Italy, surgical residents stated that clinical and surgical training activities were interrupted, and they had to leave the operating rooms to support the covid areas [34]. When we examined the examples of good practice aiming to turn the current process into an opportunity in terms of education, we did not find any examples of good practice in the literature in the context of our country. In this context, we examined studies from around the world.

The Relationship Between Burnout and Educational Environment

Residents, who have experienced significant disruptions in their education processes due to the pandemic, are under a heavy burden due to increased workload and psychosocial stress. It is estimated that this situation increases their predisposition to burnout in all dimensions. One of the factors that increase this predisposition is the educational environment. When the studies on the factors associated with the burnout levels of resident physicians are reviewed, it has been observed that residents' perceptions about the educational environment significantly affect their

burnout levels [21,22,35,36]. In this study, we found that residents' negative perceptions about different dimensions of the educational environment showed a positive relationship with all three dimensions of burnout (Table 6).

In a study from Thailand, 88% of the pediatric residents had a positive perception of their role autonomy, 51% thought that teaching activities needed some improvement, and for the social support, most (85%) thought that there were more pros than cons [37]. When this study is compared with the results of our study, it has been shown that resident physicians' perceptions of various dimensions of the educational environment were more positive and not associated with burnout. However, in the findings obtained from qualitative interviews with residents to revealed that trainers and teaching styles, feelings of inadequacy related to the level of knowledge, assignments that are not related to the education come to the fore as educational environment variables associated with burnout [37].

In our study, the emotional exhaustion sub-dimension of burnout emerged as the most strongly related sub-dimension with perceptions of the educational environment. The depersonalization sub-dimension was only moderately associated with the perception of low role autonomy. The low personal achievement sub-dimension of burnout, on the other hand, showed a moderate-high correlation with all the components related to the educational environment and showed the most substantial relationship with the perception of low social support. In a study conducted in Greece, perceptions about the hospital education environment were statistically negatively correlated with the level of burnout [38]. This shows that the positive evaluation of the clinical learning environment is inversely proportional to the burnout levels. In the same study, it was observed that social support, one of the PHEEM subscales, was negatively associated with burnout. At the same time, autonomy and teaching sub-dimensions were significantly and negatively related to burnout. The residents stated that the most crucial stress factor leading to high burnout was workload [36].

In our study, the perception of social support showed a significant relationship with all burnout dimensions. Social support also includes relationships with seniors, peers, and educators in the hospital environment where learning and service delivery occur together [26]. Vendeloo et al. [21], in their study with orthopedic residents in Belgium, concluded that the learning environment feature that showed the most vital relationship with burnout symptoms was weak peer collaboration. A study conducted in Greece showed that peer interaction was negatively correlated with low personal achievement sub-dimension of burnout, in line with the results of our research results. In the same study, it was found that those who think that the trainers, which is another essential component of social support, value to postgraduate education, show less burnout in all sub-dimensions [39]. These researches and ours suggest that both the peer relationship and the support relationship established with the educators are protective against burnout. However, due to the assignments in the COVID-19 clinics and intensive care units, many residents have been away from the learning environments where they received specialty training during the COVID-19. Contact with peers and seniors in the same specialty or with faculty members has decreased considerably. It has also become impossible for residents to receive feedback due to limited training opportunities. This may be why the perception of social support of most resident physicians participating in our study was not satisfactory. Peer and faculty member interaction, which is one of the most important determinants of social support, should be supported and increased regardless of the circumstances.

In this study, having a negative perception of professional autonomy was associated with all dimensions of burnout. In parallel with these results, Zubairi [40] revealed the relationship between lack of autonomy and burnout in his study with resident physicians from different fields. Papaefstathiou et al. [38] found the PHEEM autonomy sub-dimension significantly and negatively related to burnout's personal and work-related exhaustion sub-dimensions (CBI scale). There are also studies in the literature that have not found a relationship between the perception of low autonomy and the level of burnout [22,35]. Efforts to train competent specialist physicians require balancing supervision and autonomy. Professional autonomy supports the intrinsic motivation of individuals and prevents

burnout. Given the opportunity for autonomy, the residents reason, develop a plan and take charge of his patient [41]. It is essential for faculty members to recognize their residents and support their autonomy with tasks appropriate to their proficiency level and the characteristics of the educational environment.

Negative perceptions of all three dimensions of the educational environment have shown the most vital relationship with the emotional exhaustion sub-dimension of burnout. Papaefstathiou [38] stated that negative perceptions about the quality of education (measured by the PHEEM scale) were significantly and negatively related to personal and work-related burnout (measured by the CBI). Puranitee [37], on the other hand, did not find a relationship between perception of educational quality and burnout. In our study, the emotional exhaustion scores of residents who reported that the education-service balance was dominant in the direction of service were higher than those who noted that the balance was prevalent in the order of education. This finding parallels that those with more negative perceptions of the educational environment showed more emotional burnout. This result suggests that one of the reasons for the negativity related to the educational environment is the greater emphasis on service than education. Similarly, Ferguson et al. has associated poor service-education balance with high burnout levels [22].

Consequences of Burnout

Since the research was conducted during the COVID-19 pandemic, new challenges have been added to postgraduate education. It should be taken into account that residents' perceptions of their educational environment may have been significantly affected by the challenges associated with the pandemic.

In this study, some factors related to burnout (the characteristics of psychosocial and residency training) that have significant consequences for residents' physical and mental health and the patients they serve were investigated. It was seen that the features most associated with burnout were related to the educational environment and burnout levels were related to negative perceptions of the educational environment. Still, it should be taken into account that this relationship may be bidirectional. The unbalancing education service during the pandemic period and the disruptions in the education environment may have contributed to the burnout of the residents. In addition, it should be taken into account that burnout may have caused negative perceptions and dissatisfaction with educational environments.

In our study, it was seen that the negative perceptions of residents about the educational environment during the pandemic period led to a decrease in their organizational commitment with the departments and institutions where they received training and worked and this decrease was associated with higher levels of burnout and low self-esteem. Additionally, residents who stated that they would prefer a different specialty and institution if they had the chance had high burnout levels and had lower self-esteem levels (Table 6). Based on these results, it is impossible to infer the direction of the relationship between burnout and organizational commitment since the study is cross-sectional. However, it was thought that their negative perceptions about the educational environment mediated the relationship between burnout and organizational commitment. Improvement of the educational environment will reduce the risk of burnout by contributing to the organizational commitment of residents and positively affecting their professional identities and self-esteem, which is a concept closely related to their professional identities.

Burnout of residents negatively affects their own physical and mental well-being and reduces the efficiency of the health care they provide to patients. In this study, 30.7% of the participants perceive their health as moderate/poor and showed higher burnout in all sub-dimensions. Burnout, which is associated with a decrease in the ability to empathize with the patients served, a reduction in the motivation to work, and an increase in medical errors, directly affects the health service delivery. In a systematic review [7], it was stated that the increase in the burnout level of residents negatively affects patient safety and quality health care delivery. Another study [42], emphasized that burnout in residents increased medical errors, and increased medical errors deepened burnout. Interventions to prevent burnout of residents during postgraduate education are significant for their wellness and the patients they serve.

According to the Turkish Medical Association research conducted in our country before the COVID-19 pandemic, it was determined that two out of three assistant physicians worked 9-12 hours a day on weekdays [43]. According to the same study, it was determined that working hours negatively affected the social lives of three out of four residents. It is essential to organize work hours to protect the physical and mental health of residents. The excessive workload can negatively affect physical and mental health, making it impossible to spare time for social life and causing adverse health effects through burnout. Considering the uncertainties in working conditions, sudden assignments, and the workload in the pandemic areas during the COVID-19 process burnout is an issue that should be taken into account by faculties, associations, the Ministry of Health.

Limitations

Only 99 (15.7%) of 632 residents in clinical specialties participated in the study and great proportion (77.8%) of the participants were from medical branches (12.1% from surgical branches). The research coincided with the pandemic period (between 7-10 months), in which the number of COVID-19 cases and deaths accelerated in our country . In addition to the responsibilities of the residents regarding the education and working environment in their departments, additional responsibilities related to their assignments in the COVID-19 fields, the significant increase in the workload, and the lack of motivation may have caused low participation in this research. All these reasons constitute limitations of the study.

CONCLUSION

In this study, we found that residents, perceptions about the educational environment are the variable most closely related to their burnout levels. The educational environments and well-being of residents, which may be related to their burnout, need to be constantly evaluated and improved. In this extraordinary period, there is a greater need for innovative teaching methods and the guidance of accreditation institutions to ensure residents' competencies.

Action plans to deal with the challenges posed by large-scale emergencies such as the COVID-19 pandemic must be ready in advance. There is a need for plans to increase the communication between residents, faculty members, institution directors, and social support. Today, we should consider burnout not as an individual problem caused only by personal factors but as a process that originates from the work environment and organizational culture and negatively affects the health service of the entire institution.

Author contribution

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

Ethical approval

The study was approved by the Hacettepe University Non-Interventional Ethics Committee (Protocol no. 20/168).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Retrospective Evaluation of Liver and Kidney Functions in Patients with Chronic Occupational Lead Intoxication Treated with EDTA Chelation Therapy*

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ABSTRACT

Objective: This study aimed to investigate hepatic and renal functions in patients who received calcium disodium edetate ($CaNa_2EDTA$) chelation treatment for chronic occupational lead intoxication.

Material and Methods: This single-center retrospective descriptive research was conducted in a secondary-level health facility. The study included patients treated with $CaNa_2EDTA$ chelation for chronic occupational lead intoxication between September 15, 2020, and May 31, 2021. Demographic and occupational characteristics, as well as and laboratory parameters obtained before and after the chelation therapy were evaluated.

Results: All 75 patients were male, and 73.3% had an occupation in metal scrap recycling. Renal parameters were within normal range before and after the chelation. However, mild elevations were observed in liver parameters. After the adjustment for demographic and occupational variables, the odds of having an elevated liver parameter and an elevated alanine transaminase (ALT) result after the chelation therapy were 9.3 (95%CI 2.6–33.2, p<0.001) and 11.4 (95%CI 2.4–53.2, p<0.001) for patients with pre-chelation elevated any liver parameter and pre-chelation elevated ALT result, respectively.

Conclusion: The current study documented mild elevations of the liver parameters in patients with chronic occupational lead poisoning after $CaNa_2EDTA$ chelation therapy, particularly those with elevated basal liver parameters, although their renal parameters stayed within reference ranges. The results serve as an example of the safe application of $CaNa_2EDTA$ chelation for chronic occupational lead poisoning, by monitoring kidney and liver parameters in a secondary-level health facility. Future prospective studies with structured treatment protocols may investigate the risk and determinants of hepatic and renal adverse effects.

Keywords: occupational disease, lead poisoning, chelation therapy, edetic acid.

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* The preliminary results of this study were presented as an oral presentation at the 3rd International Industrial and Environmental Toxicology Congress, which was held between November 4-10, 2021, as a virtual congress.

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INTRODUCTION

Lead (element symbol, Pb) is a heavy metal with an atomic number of 82. Lead has been used since ancient times and is one of the most toxic environmental pollutants [1]. One of the primary causes of lead exposure to humans has been occupational. The exposure may occur in a wide range of work activities, including mining and extraction of the lead from ores, as well as manufacturing processes using lead alloys (e.g., batteries and plumbing components) or lead compounds (e.g., painting pigments), and recovery from lead-containing material or scrap [2].

The biological effects of lead on human health are diverse. Lethal effects are observed upon acute high-dose intoxication, but lead may also chronically affect central and peripheral nervous, cardiovascular, hematological, musculoskeletal, urinary, hepatic, gastrointestinal, and reproductive systems, according to exposure level [3]. Although the primary approach should be the prevention of exposure by health and safety measures applied according to a hierarchy of controls [4], chelation treatment of acute or chronic lead intoxication may be required [5]. The purpose of chelation therapy is to bind to the toxic metal, thereby capturing it in a less toxic substance form, for subsequent excretion [6]. An ideal chelator is defined as having a greater affinity with the metal and providing rapid elimination, as well as showing only low-level side effects [7].

Calcium disodium edetate ($CaNa_2EDTA$) has been one of the agents used in chelation treatment for lead poisoning since the 1950s [8]. It can be applied either through the intramuscular or intravenous routes, but it is usually advisable to monitor its application with biochemical tests during the course of treatment due to possible side effects [9]. The situation may become more complex, as chronic lead intoxication may result in the deterioration of kidney and liver functions [10]. However, data on renal and hepatic functions in Turkish patients with chronic lead poisoning treated with $CaNa_2EDTA$ are scarce. Therefore, this study aimed to evaluate hepatic and renal functions in patients who received $CaNa_2EDTA$ chelation treatment for chronic occupational lead intoxication.

MATERIALS AND METHODS

Study design, subjects, variables

This single-center retrospective descriptive study was conducted in a secondary-level health facility, namely Ankara Occupational and Environmental Diseases Hospital, located in Ankara, Turkey. The inclusion criterion was a positive history of treatment with $CaNa_2EDTA$ chelation for chronic occupational lead intoxication in Ankara Occupational and Environmental Diseases Hospital between September 15, 2020, and May 31, 2021. Exclusion criteria were missing pre- or post-chelation data, and unplanned treatment interruption due to the patient's demand.

The hospital's scheme for $CaNa_2EDTA$ chelation treatment included cycles of intravenous infusions for a daily dose of 30–50 mg per kilogram of body weight for five days, and one or two days of break in between, if subsequent cycles were needed. The daily dose was given in two infusions, each lasting approximately 4 hours. The scheme also included laboratory monitoring, i.e., biochemical tests and blood lead levels, on the third day and at the end of the cycle, to decide whether treatment should be continued or finished.

The collected data were age, sex, body weight (in kg), height (in cm), body mass index (in kg/m2), duration of exposure, number of chelation treatment cycles, serum levels of alanine transaminase (ALT, in U/L), aspartate transaminase (AST, in U/L), gamma-glutamyl transferase (GGT, in U/L), direct and total bilirubin (in mg/dL), creatinine (in mg/dL), blood urea nitrogen (BUN, in mg/dL), and blood lead levels (in mg/dL) both before and after the chelation. Elevated values for creatinine, BUN, ALT, AST, GGT, and direct and total bilirubin were determined based on laboratory reference values.

Statistical analysis

Descriptive statistics are shown as numbers and percentages for categorical variables. The normality of the continuous variables was analyzed using the Shapiro–Wilk test, and means with standard deviation (SD), or medians with interquartile range (IQR) values were given accordingly. The pre- and post-chelation laboratory parameters of patients were compared using the paired samples t-test or Wilcoxon signed-rank test for continuous variables.

The pre- and post-chelation liver parameters were also compared as normal versus elevated, using the McNemar test. The significant associations between elevated results pre- and post-chelation were analyzed using logistic regression models with adjustment for age, BMI, lead blood level pre-chelation, duration of exposure, and the number of treatment cycles. The odds ratio (OR) values together with 95% confidence interval (95%CI) were calculated. Type 1 alpha was accepted as 0.05 for all analyses, which were performed using IBM SPSS for Windows v.22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The study included data from 75 male patients. The demographic, occupational, and treatment characteristics of patients are shown in Table 1. The median values were 31 years (IQR 25–39) for age, and 24.7 kg/m2 (IQR 22.7–29.0) for BMI. Eighty percent of subjects were current smokers, and an additional 6.7% were ex-smokers. There were no patients with pre-existing kidney disease. There was one patient with hepatitis B surface antigen positivity. The median duration of occupational lead exposure was 24 months (IQR 7–36). The most common occupation among patients was metal scrap recycling (73.3%), followed by battery production, foundry, lead extraction from ores, and arms industry. The chelation therapy was completed in all patients by achieving treatment goals.

The comparison of laboratory results pre- and post-chelation, shown in Table 2, depicted a statistically significant difference in blood lead level, creatinine, BUN, ALT, GGT, and total and direct bilirubin. The pre- and post-chelation median values were 59.1 µg/dL (IQR 45.3–68.0) vs 19.1 µg/dL (IQR 15.3–24.5) for blood lead level (p<0.001), 13 mg/dL (IQR 11–16) vs 10 mg/dL (IQR 9–12) for BUN (p<0.001), 23 U/L (IQR 18–28) vs 24 U/L (IQR 17–33) for ALT (p=0.001), 21 U/L (IQR 14–29) vs 27 U/L (IQR 18–51) for GGT (p<0.001), 0.11 mg/dL (IQR 0.08–0.13) vs 0.10 mg/dL (IQR 0.07–0.12) for direct bilirubin (p=0.001), and 0.60 mg/dL (IQR 0.47–0.78) vs 0.50 mg/dL (IQR 0.38–0.65) for total bilirubin (p<0.001). The mean creatinine values were 0.74 mg/dL (SD=0.11) before the treatment and 0.77 mg/dL (SD=0.10) after the chelation (p=0.002).

Table 1. Demographic, occupational, and treatment characteristics

Characteristic	Value
Age, year, median (IQR)	31 (25-39)
Height, cm, median (IQR)	175 (170-180)
Weight, kg, mean (SD)	78.9 (14.5)
BMI, kg/m^2, median (IQR)	24.7 (22.7-29.0)
Smoking status, n (%)	
Never smoker	10 (13.3)
Ex-smoker	5 (6.7)
Current smoker	60 (80.0)
Duration of exposure, month, median (IQR)	24 (7-36)
Occupation, n (%)	
Metal scrap recycling	55 (73.3)
Battery production	7 (9.3)
Foundry	6 (8.0)
Lead extraction from ores	4 (5.3)
Arms industry	3 (4.0)
Number of chelation therapy cycles, median (IQR)	2 (1-3)

BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Table 3 demonstrates the comparison between pre- and post-chelation liver parameters, including ALT, AST, GGT, and total and direct bilirubin, regarding laboratory reference values. Twenty-three (30.7%) patients had at least one elevated parameter before chelation, but 33 (44.0%) had at least one elevated parameter after chelation (p=0.041). The number of patients with elevated liver levels was 15 (20.0%) for ALT, 4 (5.3%) for AST, 10 (13.3%) for GGT, 2 (2.7%) for direct bilirubin, and 4 (5.3%) for total bilirubin before chelation. After chelation, the number of patients with elevated liver levels was 27 (36.0%) for ALT, 10 (13.3%) for AST, 15 (20%) for GGT, 2 (2.7%) for direct bilirubin, and 2 (2.7%) for total bilirubin. There was a statistically significant difference between the percentages of patients with elevated ALT levels (p=0.008) pre- and post-chelation. Regarding the case with hepatitis B surface antigen positivity, the patient did not show any elevated results before or after chelation therapy. Although a higher median creatinine but a lower median BUN were observed after the chelation, there were no patients with levels above reference ranges for both parameters pre- or post-chelation.

The relationship between any liver parameter elevated post-chelation and elevated ALT levels with elevated results pre-chelation was evaluated with logistic regression analyses (Table 4). After the adjustment for age, BMI, lead blood level pre-

chelation, duration of exposure, and the number of treatment cycles, elevations in any liver parameter and ALT after the chelation were related to any liver parameter (adjusted OR [aOR]=9.3, 95%CI 2.6–33.2, p<0.001) and ALT level (aOR=11.4, 95%CI 2.4–53.2, p<0.001) elevated pre-chelation, respectively.

Table 2. Comparison of pre-and post-chelation laboratory parameters

Characteristic	Pre-chelation	Post-chelation	p-value
Blood lead level, µg/dL, median (IQR)	59.1 (45.3-68.0)	19.1 (15.3-24.5)	**<0.001***
Creatinine, mg/dL, mean (SD)	0.74 (0.11)	0.77 (0.10)	**0.002†**
BUN, mg/dL, median (IQR)	13 (11-16)	10 (9-12)	**<0.001***
ALT, U/L, median (IQR)	23 (18-28)	24 (17-33)	**0.001***
AST, U/L, median (IQR)	26 (15-36)	35 (20-54)	0.267*
GGT, U/L, median (IQR)	21 (14-29)	27 (18-51)	**<0.001***
Total bilirubin, mg/dL, median (IQR)	0.60 (0.47-0.78)	0.50 (0.38-0.65)	**<0.001***
Direct bilirubin, mg/dL, median (IQR)	0.11 (0.08-0.13)	0.10 (0.07-0.12)	**0.001***

Bold p-values indicate statistical significance. ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; GGT, gamma-glutamyl transferase; IQR, interquartile range; SD, standard deviation.

*Wilcoxon signed-rank test

†Paired samples t-test

Table 3. Comparison of pre-and post-chelation liver parameters according to elevation status

Pre-chelation measurement	Post-chelation measurement		p-value*
	Normal	Elevated	
Any liver parameter, n (%)			**0.041**
Normal	37 (71.2)	15 (28.8)	
Elevated	5 (21.7)	18 (78.3)	
ALT, n (%)			**0.008**
Normal	45 (75.0)	15 (25.0)	
Elevated	3 (20.0)	12 (80.0)	
AST, n (%)			0.146
Normal	62 (87.3)	9 (12.7)	
Elevated	3 (75.0)	1 (25.0)	
GGT, n (%)			0.125
Normal	59 (90.8)	6 (9.2)	
Elevated	1 (10.0)	9 (90.0)	
Total bilirubin, n (%)			0.625
Normal	70 (98.6)	1 (1.4)	
Elevated	3 (75.0)	1 (25.0)	
Direct bilirubin, n (%)			1.000
Normal	72 (98.6)	1 (1.4)	
Elevated	1 (50.0)	1 (50.0)	

Bold p-values indicate statistical significance. ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase.

*Mcnemar test

Table 4. Logistic regression analysis of post-chelation elevation in liver parameters

Parameter	Crude		Adjusted*	
	OR (95% CI)	p-value	aOR (95% CI)	p-value
Post-chelation elevated any liver parameter				
Pre-chelation elevated any liver parameter	8.9 (2.8-28.3)	**<0.001**	9.3 (2.6-33.2)	**<0.001**
Post-chelation elevated ALT				
Pre-chelation elevated ALT	12.0 (3.0-48.4)	**<0.001**	11.4 (2.4-53.2)	**<0.001**

Bold p-values indicate statistical significance. ALT, alanine transaminase; aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

*Adjusted with age, body mass index, pre-chelation blood lead level, duration of exposure, and number of treatment cycles

DISCUSSION

This study evaluated hepatic and renal functions of 75 Turkish patients treated with $CaNa_2EDTA$ chelation for chronic occupational lead poisoning. Their main occupation was metal scrap recycling (73.3% of patients). A statistically significant difference was detected in lead blood level, creatinine, BUN, ALT, GGT, and total and direct bilirubin obtained before and after the treatment. Although renal parameters were within normal range before and after the chelation, mild elevations were observed in liver parameters. The odds of having an elevated liver parameter and elevated ALT after the chelation therapy were 9.3 and 11.4, for patients with any liver parameter elevated pre-chelation and ALT elevated pre-chelation, respectively, after adjustment for age, BMI, lead blood level pre-chelation, duration of exposure, and the number of treatment cycles.

The findings demonstrated that the most common occupation among patients was metal scrap recycling. A review on lead exposure in developing countries with low or middle income defined various high-exposure work activities, including the manufacture of wares, jewelry, and decorative items (due to production and application of lead-containing glazes), battery production, demolition, welding, automobile radiator repair, and electronic waste recycling [11]. Koh et al. evaluated articles published between 1940 and 2010 in the United States, and found that most measurements were sourced from lead-based painting, joining, or cutting metals by heat, metal manufacturing, and battery production [12]. With regard to the situation in Turkey, a previous study from our hospital also demonstrated that most of the patients with lead exposure worked at a recycling facility [13]. Kuman-Oyman et al. evaluated patients diagnosed with lead intoxication in the Istanbul Occupational Diseases Hospital (Istanbul, Turkey) between 2012 and 2018, and showed that the most frequent employment sector was the production of electronic tools and devices [14]. Although battery production was the second most common occupation in the current study, this industry is also important for developing countries with higher lead blood levels in workers [15]. These findings are important in the surveillance part of occupational health and safety activities, to prioritize the risk groups for receiving planned interventions.

Before and after the treatment, lead blood level, serum creatinine, and blood urea nitrogen were statistically significantly different. Lower lead blood levels after the therapy were expected with regard to the purpose of chelation [16]. Effects of the $CaNa_2EDTA$ chelation on renal parameters has been defined as critical [9, 17]. Although this type of adverse effect is not common, the $CaNa_2EDTA$ chelation was related to elevations in serum creatinine and blood urea nitrogen [9]. However, a possible role of $CaNa_2EDTA$ chelation in slowing down the decline in renal function in patients with chronic kidney disease and lead exposure history has been documented [18]. Findings of the present study did not show any elevated results in serum creatinine and blood urea nitrogen. This may result from a well-designed treatment protocol regarding treatment goals (i.e., number of cycles and target lead blood level). Moreover, one- or two-day breaks were implemented to avoid treatments for more than five days, as advisable against nephrotoxicity [9].

Results showed a statistically significant difference in ALT, GGT, total, and direct bilirubin levels obtained before and after the treatment. Furthermore, for patients with elevated results pre-chelation, mildly elevated post-chelation results were observed in liver parameters, with the odds of any liver parameter elevated post-chelation and elevated ALT level being 9.3 and 11.4, respectively. The elevation in liver transaminases with $CaNa_2EDTA$ chelation was defined as mild, and expected to return to normal levels after the cessation of treatment [19]. A French study observed transient transaminase elevations in two of fourteen patients receiving $CaNa_2EDTA$ for lead poisoning [20]. The authors considered these elevations related to alcohol consumption in one patient and the acute nature of intoxication in the other. The current study also depicted that elevated liver parameters after the chelation therapy were related to elevated pre-chelation results. These results point out the importance of monitoring liver parameters during the $CaNa_2EDTA$ chelation in patients, particularly those with elevated basal liver parameters.

This study's strength included the evaluation of various parameters related to renal and hepatic functions, comparison of post-chelation results with those obtained before the treatment, and statistical analysis with an adjustment for parameters related

to lead exposure and chelation treatment. However, the current study has some limitations. First, results did not include intermittent measurements of renal and hepatic parameters during the course of treatment, despite the comparison of pre- and post-chelation values. Second, symptoms and signs related to chronic lead poisoning were not analyzed. Moreover, the exposure levels of patients could be related to pre- or post-chelation measurements. Although this limitation was partially eliminated by evaluating the duration of exposure, a detailed approach would be more beneficial. Lastly, due to the retrospective nature of the study, a detailed protocol with a follow-up component was not applied. Future prospective studies may overcome this issue.

In conclusion, this study documented mild elevations of liver parameters in patients after $CaNa_2EDTA$ chelation therapy, particularly those with elevated basal liver parameters, although patients' renal parameters stayed within reference ranges. These results serve as example of the safe application of $CaNa_2EDTA$ chelation for chronic occupational lead intoxication, by monitoring kidney and liver parameters in a secondary-level health facility. Future prospective studies with structured treatment protocols may investigate the risk and determinants of hepatic and renal adverse effects.

Author contribution

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

Ethical approval

This study has been conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Yuksek Ihtisas University Non-Interventional Ethics Board (Protocol no. 2021/14/01, August 25, 2021).

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Conflict of interest

The author declares that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Clinical Features and Treatment Results of Conjunctival Melanoma: Cross-Sectional Study

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ABSTRACT

Purpose: Our aim in this study is to report the clinical features and treatment results of patients with conjunctival melanoma (CM) diagnosed in our clinic in the last 20 years.

Materials and Methods: Demographic information, tumor diameter, accompanying melanosis, presence of recurrence and survival data were obtained retrospectively from the records of patients who had histopathologically confirmed CM diagnosis.

Results: Conjunctival melanoma was detected in 84 eyes of 84 patients with a mean age of 61.5±24.6 years. In total 45.2% of the patients were female and 54.8% were male. The two most common primary lesion locations were limbus in 23.8% and bulbar conjunctiva in 22.6% of the patients. In ophthalmological evaluation, 46.3% of the patients had concomitant primary acquired melanosis. Appropriate surgical excision to the extent of the disease was performed primarily in all patients. After a median follow-up of 55 months, local recurrence rate was 45.2%, while the survival rate was found to be 74.3%.

Conclusion: Conjunctival melanoma is a malignant neoplasm seen in advanced adulthood, often involving the bulbar surface of the conjunctiva. Even using the standard surgical approach, CM is associated with a 45.2% local recurrence rate and a 25.7% mortality rate. In our study, there was no clinical parameter that showed a statistically significant relationship with survival.

Keywords: Conjunctiva, melanoma, excision, cryotherapy.

INTRODUCTION

Conjunctival melanoma (CM), constituting approximately 5% of all ocular melanomas, is a malignant ocular surface tumor that is formed by malignant transformation of normally residing conjunctival melanocytes [1]. Population-based studies in the literature present findings that CM incidence has been increasing over time [2,3]. Conjunctival melanoma, which constitutes approximately 25% of melanocytic conjunctival tumors, is most commonly seen in Caucasians [4]. Conjunctival melanoma may arise either from primary acquired melanosis (PAM), conjunctival nevus or occur de novo [5]. In addtition to the basic principle in the primary treatment of CM being surgical excision performed with no-touch technique; local recurrence, distant metastasis and even death are not uncommon despite appropriate surgery [1,5,6]. Our aim in this study is to report the findings and treatment results of CM patients who were diagnosed and treated in our hospital which serves as a tertiary health care clinic in our country.

MATERIALS AND METHODS

Patients who applied to Hacettepe University Faculty of Medicine, Ocular Oncology Service and received histopathological diagnosis of CM between October 2000 and October 2020 were included in the retrospective cross-sectional study. The study was approved by Hacettepe University Non-Interventional Clinical Research Ethics Committee with decision number 2019/17-52. The study was conducted in accordance with the Declaration of Helsinki.

Patients' information obtained from Hacettepe University electronic data system, Ocular Oncology Service records and anterior segment photographic archive included: age at diagnosis, gender, location of the primary lesion, base width of primary lesion in clock hours, distance of the lesion's closest border to limbus, presence of accompanying PAM, extent of PAM if present, degree of pigmentation of the primary lesion, treatment of the primary lesion, presence of local recurrence, survival status and duration of follow-up. If a multifocal lesion was observed at the time of admission, the characteristics of the largest lesion were recorded.

In confined lesions with a base width of less than 1 cm, lesion localization was categorized in 4 classes as: limbus, bulbar conjunctiva, tarsal conjunctiva or caruncle (Figure 1). Because of the involvement of more than one category, this classification was not applied in more diffuse or giant tumors where the base of the lesion was larger than 1 cm. Additionally, the base width of tumors in which the base of the tumor could be evaluated was noted in clock hours. The extent of PAM was defined as focal in cases of involvement less than ¼ of the total conjunctival surface, and diffuse in cases of more extensive involvement (Figure 1).

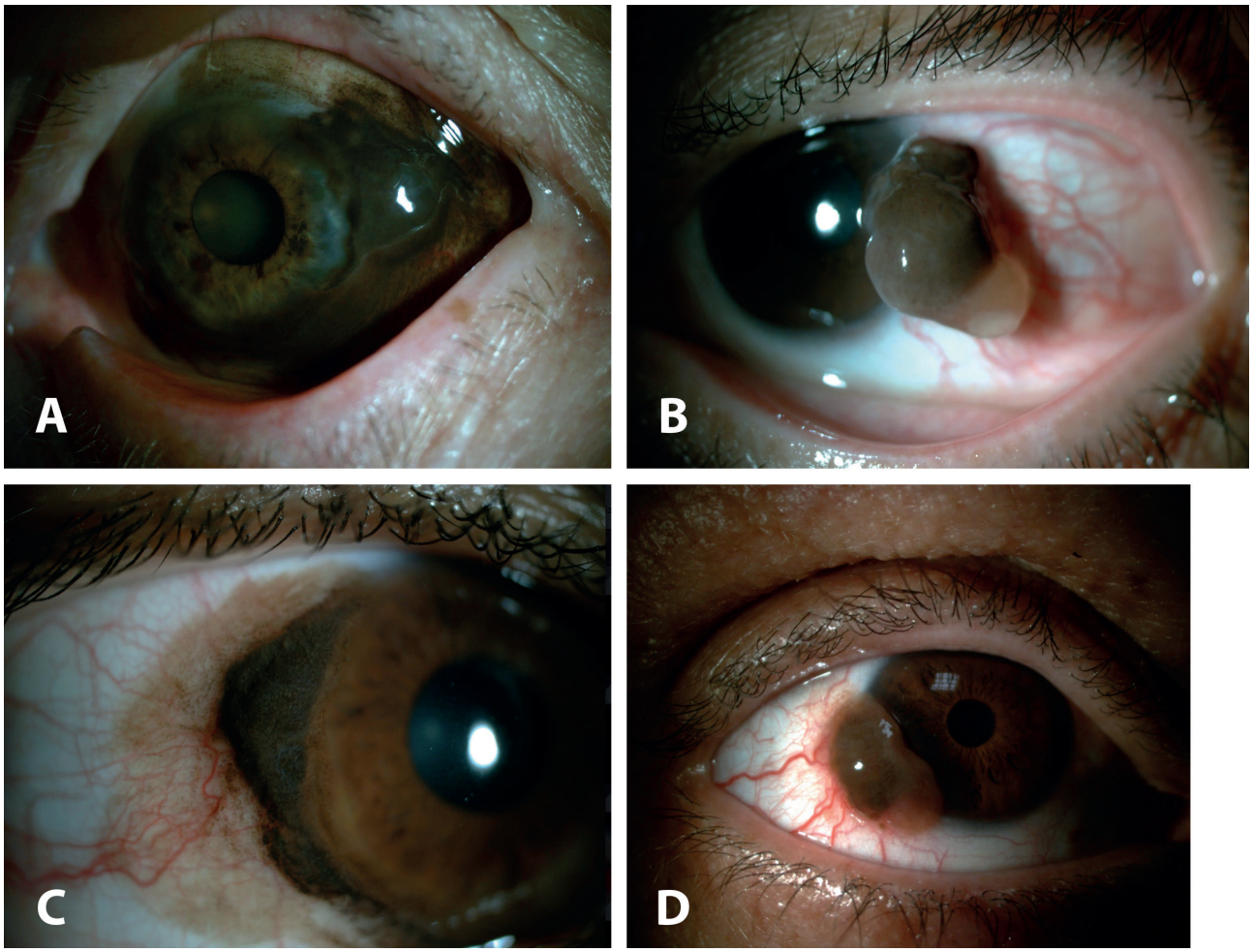

Figure 1. A. Diffuse melanoma with a wide base **B.** Melanoma with a mixed pigmentation pattern **C.** Limbal melanoma with diffuse primary acquired melanosis **D.** Melanoma with a dilated feeder vessel, as decribed in the study.

In our clinic, surgical removal is adopted as the gold standard in the treatment of CM and its recurrences. In cases where there is no clinical suspicion of scleral or orbital invasion, surgical principles defined in the literature aiming negative surgical margins were used as standard treatment of CM.6 Enucleation and orbital exenteration were offered in the presence of deep scleral invasion or intraocular invasion or in the presence of orbital involvement, respectively. If the histopathological surgical margin was positive adjuvant topical IFNα2β or 5-FU were used until 2018 and after 2018, respectively, due to the difficulties in the supply of IFNα2β following 2018. Dosing schedule was arranged on a patient basis.

In the study, IBM SPSS Statistics for Windows program was used for descriptive statistics and Kaplan Meier analysis (Version 23, IBM Corp., Armonk, N.Y., USA). In descriptive statistics mean and standard deviation or median and range of values were included. T-test and Mann-Whitney U test were used to compare the quantitative data with and without normal distribution between the two groups, respectively.

RESULTS

A total of 84 eyes of 84 patients were analyzed retrospectively. Of the patients, 38 (45.2%) were female and 46 (54.8%) were male. The mean age of the patients was 61.5±24.6 years (range: 22-100), and there was no statistically significant difference between genders (p=0.680). Primary lesion localization was limbus in 20 patients (23.8%), bulbar conjunctiva other than limbus in 19 patients (22.6%), caruncle in 7 patients (8.3%), and palpebral conjunctiva in 5 patients (6.0%). Tumors involving more than one of these compartments were encountered in 20 patients (23.8%). While PAM was present in 25 (46.3%) of anatomically limited tumors in which the presence of PAM could be evaluated, it was not observed in 29 cases (53.7%). Of 25 patients with PAM, focal PAM was detected in 10 (40.0%) and diffuse PAM (60.0%) in 15. In patients whose primary tumor pigmentation could be evaluated, 40 (66.7%) had melanotic, 6 (10.0%) showed amelanotic and 14 (23.3%) had tumors with both melanotic and amelanotic components. In tumors where the base of the lesion could be evaluated in terms of clock hours, the median tumor diameter was found to be 4 (range: 1-12). Excluding the tumors primarily located at the limbus, median distance from closest corneal side to limbus was 3.5 mm (range: 0.5-13.0). Multifocal tumors at the time of admission were seen in 4 (4.8%) patients. One (1.1%) patient had enucleation due to recurrence with intraocular spread, 2 (2.4%) patients had primary orbital exenteration due to orbital spread at the time of admission, and two (2.4%) patients received secondary orbital exenteration due to recurrence with orbital spread during follow-up.

The median follow-up time from the initial time of diagnosis was 55 months (range: 6-250). During the whole follow-up period, local disease recurrence was observed in 14 patients (45.2%), while recurrence was not observed in 17 patients (54.8%) after initial treatment. The survival rate of the patients with follow-up data after a median of 55 months was 74.3% (n=26). The cause of death in 9 patients (25.7%) who were deceased was found to be distant metastasis of CM. Death occurred after an average of 45.9±20.7 months from the time of initial CM diagnosis. In the linear regression analysis, no statistically significant correlation was found between age, gender, location of the primary lesion, the diameter of the lesion in clock hours, the degree of pigmentation or presence of recurrence with overall survival in univariate analysis, thus further multivariate analyses were not applied.

DISCUSSION

Histologically, the conjunctival epithelium possesses a non-keratinized stratified squamous epithelium. Normally, in the basal layer of this conjunctival epithelium, melanocytes are expected to be seen in a small number and proportion compared to the basal epithelial layer cells. Benign or malignant lesions arising from these melanocytes are frequently encountered in ophthalmology practice. When lesions originating from conjunctival melanocytes are evaluated as a whole, approximately ¼ of all conjunctival melanocytic lesions are found to be CM and ¼ is described as PAM, which is considered a precursor to CM [4,7]. Clinically, CM can initially be diagnosed as a maculopapular or nodular lesion with melanotic, amelanotic or combined pigmentation as a mobile or immobile mass depending on its extent [1]. It can occur in any part of the conjunctiva and may

contain dilated feeder vessels [1]. Conventional primary treatment consists of surgical excision with 2-3 mm clear margins, with or without cryotherapy to remaining conjunctival borders [6,8]. Additional superficial sclerectomy or orbital exenteration may be preferred in cases with suspicion of superficial scleral involvement or orbital spread, respectively [6,8]. Adjuvant topical chemotherapy, plaque brachytherapy or external beam radiotherapy can be applied in case of suspected or biopsy-proven residua disease [8].

In our study, consistent with the literature, at the time of diagnosis of CM there was a slight male predominance (54.8% vs. 45.2%) with a mean age at diagnosis of 61.5 years, and no pediatric cases were observed [4].

In the literature, it has been shown that the diagnosis of PAM, which is considered a precursor of CM, occurs at a statistically earlier age than CM, supporting the chronology of CM development from PAM [4,9]. The most two common primary lesion locations are found to be limbus and non-limbal bulbar conjunctiva with 23.8% and 22.6% frequencies in the present study. These results are consistent with the expectation that 83.5% - 92% of CM would be seen on the bulbar side of the conjunctiva and the remaining 16.5% in the non-bulbar conjunctiva [8,10]. The frequency of PAM accompanying the primary lesion is 46.3%, %60 of which corresponds to diffuse PAM; however, no prognostic effect of this finding on survival was found. The extent of the lesion precluded the compartment classification and lesion diameter measurement as described above in methods in 23.8% of cases which points to advanced and extensive tumors in nearly 1/4th of our patients. For this reason, it was not possible to draw solid conclusions from comparison of our results with the larger series in the literature in which smaller CM cases accounted for a larger proportion [4,11]. Considering that in the largest series in which primary lesion involved 4.6 clock hours and the mean basal diameter is 10.8-12.5 mm, the patients who applied to our clinic presented with more advanced stages and more widespread disease [4,11].

In our study, a statistically significant regression model could not be established for the factors affecting the development of local recurrence due to the insufficient sample size. Five-year local recurrence rates in the literature vary between 26% and 66% and the recurrence rate of 45.2% seen after 55 months of follow-up in our study is consistent with these data [10-13]. When age, gender, location of the primary lesion, the diameter of the lesion in clock hours, the degree of pigmentation and the presence of recurrence were evaluated with univariate regression analysis as the clinical parameters which could possibly affect survival, no parameter showing a statistically significant relationship with survival was found. In the literature, however, various risk factors have been presented for development of CM metastasis and death. These include: positive surgical margins, tumor location outside the limbus, presence of local recurrence, tumor thickness, tumor diameter, advanced age, male gender, T4 tumors, lymph node involvement at the time of diagnosis, histopathological tumor thickness and ulceration [2,10,13-15].

The main limitations of our study include the limited number of patients and limited follow-up data. Tumor, node and metastasis classification could not be used due to high proportion of patients presenting with diffuse disease. In order to examine the factors affecting local recurrence and survival in detail, multicenter prospective studies and evaluation of additional factors such as histopathological prognostic criteria hold great importance.

CONCLUSION

Although conjunctival melanoma is a rare disease, it is a malignant tumor that should be treated and followed meticulously. Despite appropriate treatment, long-term follow-up is required in terms of local recurrence and metastasis, especially in cases presenting with advanced disease.

Author contribution

Study conception and design: İK, YK, HK; data collection: İK, YK; analysis and interpretation of results: İK, YK, HK; draft manuscript peparation: İK, YK, HK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (Protocol no. 2019/17-52).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

The Effect of Music on Procedural Analgesia and Anxiety of Patients Undergoing Diagnostic Facet Block for Low Back Pain

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ABSTRACT

Aim: Chronic back pain is a common health problem which deteriorates quality of life which may be managed by medical therapy, interventions and surgery. Interventional therapies, including facet blocks and facet denervations are used regularly. Music therapy may be used before or during the painful interventional procedures with or without sedation. The study was designed to assess the effects of listening to music on procedural analgesia and anxiety during diagnostic facet block procedure.

Method: Volunteering 52 patients that were involved in the study were randomly allocated into intervention and control groups of 26 patients each. The intervention group listened to music of their choice, if they demanded or classical music with headphones during the procedure. The control group did not listen to music. A combination of midazolam, morphine and fentanyl were used for sedation and analgesia in both groups.

Results: The majority of the patients were women (77%) and the mean age was 55. We used Numeric Rating Scale (NRS) to assess pain, Spielberger State Trait Anxiety Inventory-6 (STAI-6) to assess anxiety and Ramsay Sedation Scale to determine the clinical level of sedation. No clinical or statistical significant differences in pain scores between control and intervention groups were found, when sedation effect was corrected (p=0.68). Ramsey Sedation Scores and NRS Scores were similar. Mean STAI-6 Score s were 9.5 ± 0.611 in the intervention group and 12.5 ± 0.726 in the control group (mean ± SE). The reduction in anxiety scores was significant both clinically and statistically, when sedation effect was corrected (p=0.006).

Conclusion: Listening to music is an easy to use method that may be effective to reduce anxiety in patients with chronic low back pain during facet block procedure.

Keywords: low back pain, music therapy, anxiety, anxiolytic agents, analgesia.

INTRODUCTION

Chronic low back pain is common in adults and has distressing effects on quality of life of the patients, labor force and health expenditures. It has been reported that 25% to 45% of chronic low back pain originates from the facet joints. Interventional procedures such as nerve branch blocks, intra-articular injections, denervations are useful in patients when satisfactory relief cannot be achieved with analgesic drug treatment. Short and long-term efficacy of named interventions has been established [1]. Interventional treatment methods for low back pain are used commonly. The procedures are usually performed in operating room conditions and adequate analgesia and sedation are provided since the procedures are moderately painful.

Music has become a non-pharmacological tool that is increasingly used in clinics to increase patient comfort and reduce pain and anxiety [2]. One of the known physiological effects of music is the feeling of relaxation, and simultaneous clinically measurable blood pressure and heart rate changes have been demonstrated [3]. It is suggested that listening to music during post-surgical care, painful processes such as labor and some minor interventional procedures increases patient satisfaction and reduces pain. Music therapy can be used effectively either solitarly or concurrently with analgesic and sedative agents [4].

Music therapy is defined by the American Music Therapy Association as the use of music to achieve set goals during a course of therapy by a trained music therapist. Music therapists direct therapy according to their patients' needs, goals and perceptions of music. Live music is often present in these therapies, and patients often go beyond passive listening; this can be in the form of singing, keeping rhythm, playing an instrument or dancing [5].

Medical music, on the other hand, was described as the presentation of recorded music by the medical personnel and passive listening by the patient. Headphones are often utilized. The patient may or may not be involved in the choice of music [6].

The most distinguished and well studied effect of music therapy is anxiolysis. This effect has been observed in several studies in different settings [7-10]. Bringman's study demonstrated that music alone, was more effective than midazolam sedation in reducing anxiety in pre-operative patients, and had similar effects on pulse rate and blood pressure [11]. Considering the possible side effects of sedative drugs such as midazolam, music therapy can be recommended as an effective anxiolytic therapy in patients waiting for surgery.

It is demonstrated that music has physiological effects. The pulse rate decreases slightly, blood pressure and respiratory rate decreases, with music [6, 10]. However, there are some inconsistencies in the data of the publications reviewed, the mentioned effects are not prominent and may not have clinical significance.

There is marked variability in results of studies on music medicine. It is essential to be considerate in interpreting the results [12]. Music was found to be superior to standard care and placebo in reducing pain during needle interventions in children [13]. There is evidence about the efficacy of music in the pediatric population, in controlling prick, procedural, and postoperative pain [14]. Another use of music in medicine is the reduction of pain during medical interventions. Various studies report a decrease in pain scores, however, the discrepancy in results of different studies, manifest methodological weaknesses of some studies may lead to limitation of the evidence obtained.

In the light of this information, music therapy can be used to reduce anxiety and pain in patients who will undergo interventional procedures with or without sedation, before and after surgery. The main advantages of the treatment are that it is simple in application, non-invasive and inexpensive, does not contain any pharmacological interaction and has no known adverse effects.

In this study, it was aimed to evaluate the effect of listening to music during the procedure on patient comfort and pain in patients with chronic low back pain caused by facet joint degeneration and undergoing diagnostic facet block.

MATERIALS AND METHODS

This study was planned as a prospective, randomized, controlled study and was conducted

in a university hospital. Volunteer patients between the ages of 40 and 85 who was planned to undergo diagnostic facet block procedure for low back pain were enrolled to the study. The patients who had severe hearing loss, difficulty in verbal communication due to mental or physical reasons, an altered state of consciousness that hinders answering questions to be used in assessing pain and anxiety were excluded from the study. A total of patients 52 were included in the study. Written informed consent was obtained from all participating patients. The patients were randomly allocated to one of the two groups; intervention and control groups. During the procedure, the patients in the intervention group listened to the kind of music they would like with headphones. The music was initiated before sedation and analgesia were administered to patients in the intervention group, soon after they were brought in to the operating room. The patients in the control group did not listen to music and no earphones were used. For the patients in both groups, sedation and analgesia were administered by the anesthesiologist in charge, regardless of the group, according to the clinical condition and needs of the patient. Clinical decisions, such as the technique of the procedure and the decision to discharge the patients were up entirely to the anesthesiologist in charge of the unit.

The anxiety level was measured with the short version of the Spielberger State–Trait Anxiety Inventory (STAI-6). The original inventory included forty questions [15]; however, short forms were developed, and reliabilities were established eventually [16,17]. The inventory was translated to Turkish and found use in some medical studies [18,19].

Sedation levels of all patients included in the study were evaluated during the procedure. After the procedure was complete and the patient fully recovered from sedation, their perception of pain and comfort during the procedure were assessed, demographic data such as age, weight, gender, and the total doses sedative and analgesic administered were obtained from the patient file. Ramsay sedation score was used to evaluate sedation level, verbal numerical rating scale (NRS) was used for pain assessment, and STAI-6 scale was used for comfort-anxiety assessment. In addition, the age, gender, weight information of the patients and the drugs they took were also noted. No information was collected regarding the identity of the patients.

Ramsay sedation score was used to evaluate the sedation levels of the patients [20] to evaluate patients under sedation in the intensive care unit and has been widely used for many years. Ramsay sedation score provides an assessment that can be converted into objective data for the level of sedation, that does not vary according to the population and individuals, and that it is easy to apply. A total of six levels were established, three with the patient awake and three with the patient asleep (Figure 1).

1	Patient is anxious and agitated or restless, or both
2	Patient is co-operative, oriented, and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response to light glabellar tap or loud auditory stimulus

Figure 1. Ramsay Sedation Score

The numerical pain scale (NRS) was used to evaluate the level of pain, which, is a one-dimensional scale similar to the visual analogue scale (VAS), with the two extremes "no pain" and "unbearable pain". The intensity of pain is scored by the patient verbally, between 0-10 [21].

It is important to evaluate and follow the anxiety levels of patients in the clinic. Spielberger State-Trait Anxiety Inventory (STAI) is a widely used scale all over the world, consisting of 40 positive and negative statements about how the subject feels. Occasionally its length causes functional complexity, so it has been endeavored to develop shorter and uncomplicated but equally reliable version of the scael. STAI-6, which contains three positive and three negative statements, has been derived from STAI [16]. On the STAI-6 scale, the patient scores each of the six statements about his mood as "Not at all", "Somewhat", "Moderately so", "Very much so" (Figure 2).

Anxiety levels were evaluated using the STAI-6 scale, as it is reliable and straightforward. In STAI-6, statements 2, 3 and 6 are positive for anxiety; statements 1, 4 and 5 are negative statements that point to reduced level of anxiety. The scores of positive statements are added and the scores of

	Not at all	Somewhat	Moderately so	Very much so
1. I feel calm	(1)	(2)	(3)	(4)
2. I feel tense	(1)	(2)	(3)	(4)
3. I feel upset	(1)	(2)	(3)	(4)
4. I feel relaxed	(1)	(2)	(3)	(4)
5. I feel content	(1)	(2)	(3)	(4)
6. I feel worried	(1)	(2)	(3)	(4)

Figure 2. Spielberger State-Trait Anxiety Inventory (STAI-6)

negative statements are subtracted from the total and an anxiety score of 6-24 is obtained. Higher scores indicate elevated levels of anxiety. There is no threshold or range [17].

The data of the study was analyzed using IBM-SPSS Statistics program (version 23.0 IBM International Business Machines Inc. Armonk, NY, USA). Descriptive analyzes were performed for demographic data and drug use. Numerical variables are presented as Mean±Standard deviation ($\bar{X}$±SD), minimum and maximum values. Qualitative categorical data are presented as numbers (S) and/or percentages (%).

Linear regression analysis was performed for the statistical assessment of the effect of listening to music on pain and anxiety levels.

Sedation and analgesia was used for all patients in our study, which, may be an independent factor on both pain and anxiety scores; therefore, the sedation levels of the patients (Ramsay Sedation Score) were included in the statistical model. Two separate regression analyzes were performed in which pain scores and anxiety scores of the patients were dependent variables, and listening to music and sedation scores were studied as independent variables. [22].

There were no predetermined standard doses or combinations of sedative and analgesic drugs administered during the intervention procedures of the patients included in the study. The drug type and doses were determined by the anesthesiologist managing the procedure, according to the clinical requirements of the patient. Since it is difficult to calculate the efficacy and potency of drugs in different combinations and their independent and cumulative contribution to sedation and pain levels as a standard data, and an assessment using drug doses directly may not reflect the clinical situation, drug doses were not included in the statistical analysis. Instead, the Ramsay Sedation Score, which gives clinical information of the achieved sedation level, was used in the analysis.

Written permission was obtaied from university non–interventional clinical research ethics committee. Informed consent was obtained from volunteering patients. The study was carried out in accordance with the principles of the Declaration of Helsinki.

RESULTS

A total of 52 patients were involved in the study, of which 40 were female (76.9%) and 12 were male (23.1%). Body weight and age distributions were statisticallty indifferent in theintervention and control groups. There were no statistically significant differences between the intervention and control groups in terms of demographic data. Demographic data are given in Table 1.

Double or triple combinations of midazolam, fentanyl, and morphine were used for sedation and analgesia in patients participating in the study. Midazolam – fentanyl, and this combination was preferred in 22 patients. Fentanyl - morphine combination was used in 11 patients, midazolam -

Table 1. Demographic Data

	N (%)	Gender (M:F)	Age (Years) (Mean±SD)	Weight (Kg) (Mean ± SD)
Intervention Group	26 (%50)	4:22	53.3 ± 13.4	76.7 ± 10.2
Control Group	26 (%50)	8:18	57.8 ± 14.1	75.1 ± 12.7
Total	52 (%100)	12:40	55.6 ± 13.8	75.9 ± 11.4
			p=0.703	*p=0.504*

morphine in 6 patients, and three drugs were used in combination for 9 patients.

Drug useage for midazolam and opioids were studied separately. Equivalent opioid dose was calculated by converting each 10 micrograms of fentanyl to 1 milligram of morphine, intended for analysis of opioid utilization. The dose of midazolam and equivalent opioid dose was calculated per kilogram of patients and analyzed.

Midazolam was used at an average dose of 0.021 mg/kg in the intervention group listening to music, and 0.016 mg/kg in the control group. There was no statistically significant difference in midazolam doses (p=0.876).

The total equivalent opioid dose was 0.0827 mg/kg in the group listening to music and 0.0831 mg/kg in the control group (Table 2). There was no statistically significant difference between these doses (p=0.718).

All patients were evaluated for pain intensity during the procedure using the numerical pain scale (Table 3). All patients were evaluated for their anxiety levels during the procedure using the Spielberger State Trait Anxiety Inventory – 6 (STAI-6). It is seen that the anxiety scores obtained with the scale consisted of values between 6 and 24, with an average anxiety score of 11.25, the maximum anxiety score of 20, and minimum anxiety score of 6 (Table 3).

Sedation may be an independent factor influencing pain and anxiety scores. Since sedation was used for all patients in both groups during the procedure, linear regression analysis, a statistical model that evaluates the effect of both music listening and sedation on NRS and STAI-6 scores has been utilized (Tables 4 and 5).

When the sedation effect is corrected; a statistically significant effect of listening to music on anxiety scores was observed (p= 0.006). The mean STAI-6 scores were found to be 2.74 points lower in the intervention group (9.88±3.115) compared to the control group (12.62 ±3.699). No statistically significant effect of listening to music on pain scores was identified.

DISCUSSION

Low back pain is a complex clinical condition, which is common all over the world, frequently leading to admission to hospitals, and affecting daily life, social and psychological conditions of the patients. It also deteriorates active labor force and public health expenditures significantly [23]. Although low back pain is mostly interpreted as mechanical or idiopathic and considered as benign, the presence of many potential rare but grave etiologies may be neglected making diagnosis and treatment of these patients challenging for numerous physicians. Therefore, it is very important to make a complete and accurate assessment that includes physical and psycho-social aspects [24]. Facet joints are the source of at least 16-41% of low back pain [25]. Facet joint pain is caused by degeneration and arthritis in joint structures. Disc degeneration in the spine and facet joint degeneration are almost always observed together and at equal levels [26].

Guidelines including algorithms for diagnosis and treatment for low back pain have been published by the American College of Physicians and American

Table 2. Opioid and Midazolam Doses

	Intervention Group	Control Group	*p*
Midazolam Dose mg/kg	0.021±0.015	0.016±0.015	0.268
Equivalent Opioid Dose mcg/kg	82.7±30.7	83.1±32.4	0.718

Mean ± SD

Table 3. Sedation Pain and Anxiety scores

	Intervention Group	Control Group	Total	p
Ramsey Sedation Score	3 ± 0.133 (2-4)	3 ± 0.133 (2-4)	3 ± 0.093 (2-4)	1.000
NRS Score	5 ± 0.361 (2-8)	5 ± 0.441 (1-9)	5 ± 0.283 (1-9)	0.687
STAI-6 Score	9.5 ± 0.611 (6-19)	12.5 ± 0.726 (6-20)	10 ± 0.507 (6-20)	0.006

Median ± SE (Min-Max)

Table 4. Effect of music and sedation on pain scores (NRS), Linear Regression Analysis

	β (± SE)	p	%95 CI
Constant	6.499 (±1.193)	-	4.101 – 8.896
Listening to Music	-0.231 (±0.557)	0.681	-1.351 – 0.889
Ramsay Sedation Score	-0.757 (±0.418)	0.077	-1.597 – 0.084
Dependent Variable:	***NRS Score***	***n = 52,***	***R^2 = 0.66***

SE: Standard Error, CI: Confidence Interval

There is no statistically significant difference in pain scores between the study group and the control group as the sedation effect is corrected (p=0.681).

Table 5. Effect of music and sedation on Anxiety Scores (STAI-6), Linear Regression Analysis

	β (± SE)	p	%95 CI
Constant	13.665 (±2.045)	-	9.556 – 17.775
Listening to Music	-2.731 (±0.995)	* 0.006	-4.650 – -0.811
Ramsay Sedation Score	-0.390 (±0.717)	0.589	-1.831 – 1.051
Dependent Variable:	***STAI-6 Score***	***n = 52,***	***R^2 = 0.147***

SE: Standard Error, CI: Confidence Interval

There is a statistically significant difference in anxiety scores between the study group and the control group, as the sedation effect is correct (p=0.006).

Pain Society. The pain management in these guidelines may be classified mainly as patient's self-care and physical exercise, pharmacological treatments, interventional treatments and surgical treatments [27].

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [28] Pain may be related to the subjective, primitive protective experiences of the person in the past [29]. The way the pain is perceived and its severity differs between individuals; however, it is quite common for the same person to perceive inconsistency in pain at different instances and to demonstrate variations in response to it [30]. Chronic pain may be nociceptive, neuropathic, or a combination of both. Psychological and environmental factors play a significant role in chronic pain compared to acute pain [29].

It is often difficult to evaluate patients' pain and anxiety level and transform it into objective data; therefore, various scales have been developed for the common use of clinicians. The most commonly used methods for the assessment of pain in adults are the visual analog scale (Visual Analog Scale for Pain VAS-Pain) and the numerical pain scale (Numeric Rating Scale - NRS). In Visual Analog Scale, the patient marks the pain on a visual scale and provides the clinician a numerical VAS score or the patient typically scores the pain verbally out of ten in Numeric Rating Scale (NRS) [21]. Patients undergoing interventional procedures for low back pain, usually experience intense pain during the procedure, so sedation and analgesia are regularly used. Listening to music before or during the procedure may influence the perception pain and anxiety.

Long questionnaire forms consisting of 20-50 questions are mostly used to evaluate the anxiety status of patients; however, shorter and practical versions of these forms have been designed and put into use when rapid assessment is required or for situations where it is aimed to measure anxiety for a certain event (examination, intervention, etc.). Among them, Spielberger State-Trait Anxiety Inventory-6 (STAI-6) is a scale that is widely used and has been translated into Turkish and validated in this language [16].

It should be noted that the majority (76.9%) of the 52 patients participating in the study were women. The situation is similar in the literature, since majority of patients who admit for examination to pain clinics with low back pain complaints are women. Also, female gender is predictive for more severe low back pain [31].

In our study, three drugs (midazolam, fentanyl, morphine) were used for sedation and analgesia, and they were frequently administered in combination. Similar drug combinations are widely used on interventional sedation and analgesia [32]. Frequently midazolam – fentanyl combination

was used in the study (42%).The use of drugs in combination is intended to benefit from their different effects. For instance, midazolam is a good sedative and anxiolytic but has no analgesic properties. When used reciprocally with fentanyl, which is a strong analgesic, smooth and superior sedation and analgesia is obtained. [33,34] The most recognized adverse effect in drug combinations is the increase in side effects such as respiratory depression [32].

The diagnostic facet block procedure carried out in the pain unit is not lengthy (10-20 minutes), and the patients are asked to arouse and communicate at certain moments during the procedure to answer questions about pain localization and spread. Therefore, patients should be at a level of sedation so as to be aroused by verbal or tactile stimuli. Considering the clinical condition of the patients, sedation and analgesia was administered by the anesthetist in charge of the unit and Ramsay sedation score was sustained within the range of 2-4.

The doses of drugs used in our study were evaluated separately as midazolam and opioid groups. The total equivalent morphine dose was calculated by converting the fentanyl dose to the equivalent morphine dose. There was no difference between the doses of midazolam and opioids used in the patient groups listening and not listening to music. In a study investigating the effects of music on labor pain and anxiety, it was found that the group listening to music had lower postpartum analgesic needs [3]. No such difference was observed in our study. Studies investigating the difference between analgesic needs are limited.The drugs used during the procedure have direct consequences on pain and anxiety. That outcome should be taken into account when assessing the effect of listening to music on pain and anxiety. The effect of drugs when used in combination differs from when they are used separately. The sedative and analgesic effects of mentioned drugs are diverse, so the dose needed to achieve the targeted effect varies in particular patients. Therefore, the sedative and analgesic potency of the drugs, and consequently, their effects on pain perception cannot be determined. Instead, the Ramsay sedation score, which provides a clinical classification of the final accomplished level of sedation and analgesia in each patient, was used to as a proper tool for assessing this perplexing effect.

The treatment of preoperative anxiety is essential since it is common and leads to unfavorable outcomes. Different pharmacological and non-pharmacological interventions may be used. Non-pharmacological treatments are becoming more popular, since anxiolytic drugs maycause serious side effects. These methods include cognitive-behavioral therapy, hypnosis, music therapy, relaxation therapy, aromatherapy, and massage [35]. Music has been used in many medical disciplines to provide psychological and spiritual assistance to patients. It is suggested that listening to music may have a beneficial effect on preoperative anxiety. In the last two decades, numerous studies have been carried out on clinical role of music medicine [6,36]. It is reported that music medicine reduces the need for morphine and decreases distress after minor surgery, but it has no further influence on postoperative care [38]. The physiological and behavioral responses of pain during and after blood sampling were reduced by music therapy in premature infants [38].

There are also reports on the lack of positive outcomes of music therapy on pain and anxiety relief [39]. Vecchione et al. have not found a significant effect on pain threshold in patients listening to classical ambient music, and concluded that the positive effect of music may be attributed to a psychological effect [40]. Music was found to decrease anxiety, but not pain during ultrasound-guided core needle breast biopsy [41].

Music was found to be effective for pain related to needle insertion into a fistula in hemodialysis patients [42] Anxiety, pain, dissatisfaction was reduced in patients listening to music during colonoscopy as well as the dose of sedative medications used during the procedure [43]. As a result of a meta-analysis evaluating patients listening to music during colonoscopy, there was an improvement in patients' total satisfaction; it has been shown that there is no significant difference in pain, analgesic and anxiolytic drug doses, and the duration of the procedure [44].

There are various questions about the practice of music therapy such as the timing of music, choosing the genre of music, utilization of headphones and preselected music or the patient-selected music [8]. There is no study that gives a direct and clear

answer to these questions; however, there have been studies concerning different methods. For instance, in a study reported by Nyugen et al. [45], patients listened to music during lumbar puncture, and the patients chose the music they would listen to, not from a list or genre, but entirely on their own. Significant improvement in pain perception was observed in the patients. In another study in which music was chosen by a music therapist in the research team, pain relief was shown in the group listening to music [46].

Choosing the music by the patient or someone else may not make a significant difference in outcomes related to pain or anxiety [47]. Patients who to listen to their favorite music may have an advantage in entertaining, getting themselves lost in music, and relaxing.

The effects of listening to music during and after the procedure was compared in two studies by Nilsson U et al,. The pain was reduced in both groupsin the first report [48]. A significant reduction in pain and morphine requirement was observed in the group that listened to music only after the procedure in the latter study [49].

The mechanism by which music therapy causes these physiological and emotional alterations on patients has not been fully elucidated. The most common theory in terms of anxiety-reducing effects is that attention of the patients is directed to a relaxing issue rather than a stressful and painful incident [50]. While this may be a vital mechanism, it is not particularly apparent to explain the effect. For example, in music therapies, the therapist guides the therapy according to the patient's immediate requirements, tendencies, changes the choice of music, so that the patient participates in a more holistic process emotionally and the positive effects of the therapy are reinforced.

Neurophysiological mechanisms probably play a role in the anxiolytic and analgesic effects of music. In a study by Gillen; it has been reported that music slightly suppresses sympathetic activity by affecting the autonomic nervous system and reduces adrenergic activity [51]. In another study, it was pointed out that music triggers the limbic system and increases the release of endorphins, thus making patients feel better particularly [52]. In a study by Miluk-Kolasa et al. [53] in the preoperative period, blood sugar decreased in patients who listened to music, in contrest to an increase in blood sugar patients who did not listen to music. This effect may be attributed to the stress response of the patients.

In a report discussing the mechanisms of action, it is stated that music activates dopaminergic centers in the central nervous system, especially the nucleus accumbens, and that these reward centers may contribute to the modulation of pain by triggering opioidergic systems through many pathways [54]. Meanwhile, quite good analgesic results were obtained in patients who were conditioned to believe that music had a pain-relieving effect. This can be evaluated in a similar framework to the placebo effect; personal emotional factors, the bond established with the chosen song, and the expectation of benefit from music will affect the patient's anxiety level and pain perception [55].

When more detailed assessments are made about the patients who selected the song they want to listen to in music therapy, it may be suggested that these patient are more likely to achieve psychological benefit. The patients stated that they have a special bond with the song they chose, that it helped them in a hard moment in time formerly, and that they felt relieved and remote when they wrapped themselves up in the music. This mechanism may be similar to the reward method in cognitive-behavioral therapies [56].

In our study, no statistically or clinically significant difference between the intervention and the control group was observed on pain during the procedure as the effect of listening to music was considered ($p>0.05$).However, a clinically and statistically significant difference between the anxiety scores of the intervention and control groups was recognized during the procedure. When the sedation effect was corrected; it was observed that the group listening to music had 2.73 lower mean anxiety score than the control group ($p=0.006$). Although sedation was used for all patients; it is a considerable result that those who listen to music had lower anxiety scores.

In a study by Liu and Petrini in which they investigated the effect of music on pain, anxiety and vital signs [57], a total of 112 postoperative thoracic surgery patients were evaluated and it was noted that the pain and anxiety scores of the intervention group listening to music were reduced. It was also

found that the heart rate of the intervention group was lower than the control group. In contrast to our study, the patients listened to music not once but for three postoperative days in thirty-minute sessions. Throughout the music sessions, the patients stayed in quiet rooms without any discomforting interventions.

Hsieh et al. [2] tested the effects of music, non-musical sound, and positive conditioning on pain perception by setting up a randomized controlled trial in which calibrated noxious stimuli were given to participants with a medical temperature probe. The participants were conditioned according to the group they belonged to; informing them that music or non-musical sound is effective in the treatment of pain. As a result of the evaluation of the participants who listened to music or non-music sound during the experiment, it was observed that listening to music resulted in a decrease in pain scores, even over enhanced conditioning. It has also been noted that non-musical sound gives better results than silence.

Akbas et al. [4] investigated the effect of listening to music on pain perception in patients who underwent ESWL (Extracorporeal Shockwave Lithotripsy) and a significant decrease in pain scores in patients who listened to music was demonstrated. In their study, although no analgesic and anxiolytic drugs were used, a substantial difference in pain scores was observed between the patients that listened to music and those who did not, decreasing from 6.4 to 2.8.

In our study, there was a significant improvement in anxiety scores, similar to these studies, but no similar change was observed for pain.

In a Cochrane review published in 2013 [6], 20 studies on the issue were reviewed and it was concluded that listening to music in patients awaiting operation was as effective as sedatives on anxiety. The authors recommend the use of such a music therapy. In our study, patients listened to music during the procedure, not before the procedure, but before onset of sedation and analgesia, and the anxiety they felt during the procedure was reduced. Music therapy can be used during the procedure, as well as in patients waiting before surgery, to reduce patients' anxiety.

There are studies evaluating the effects of music on physiological values such as heart rate, respiratory rate, and blood pressure reporting that music reduces blood pressure and heart rate to some extent, despite their inconsistencies [11,53,57,58]. In a study investigating the effect of music on labor pain, it was demonstrated that both pain and anxiety of patients who listened to music was reduced, and their heart rate, blood pressure and respiratory rate decreased [3].

The genre of listened music in music therapy and the question whether the patient or the practitioner should choose the playlist has not been elucidated [45,49]. It is acclaimed that patients who form a bond with music and certain songs can achieve further constructive results if they choose the playlist themselves; however, there is also evidence that the choices made by a trained music therapist may be superior [46]. In our study, when asked about the music they want to listen, about half of the patients in the music-listening group either did not state any preference or they used very broad expressions such as "joyful songs" or "folk songs". Only a few patients had a completely definitely clear selection of artists or songs. For patients who do not declare specific musical preference, it may be useful for the practitioner to play selected songs, rather than making random choices.

CONCLUSION

The therapeutic effects of listening to music on emotional state, anxiety and pain are known. There is increasing evidence suggesting music therapy may reduce both pain and anxiety during painful procedures.

In this study, we investigated the effects of music on the pain and anxiety associated with the procedure in patients who received interventional treatment for low back pain. We found no statistically significant change in the pain scores of patients who listened to music, but a significant reduction in their anxiety scores. Even though all patients in our study were sedated, the decrease in anxiety scores in the group listening to music is noteworthy.

Music is an easily accessible and inexpensive method that may be individually adapted to the patient and conducted without negative effects. It

may be used as an effective anxiolytic in patients awaiting preceding surgery, during the procedure or in the early postoperative period in patients undergoing interventional procedures with or without sedation. Further studies with higher number of patients may be planned and the type of music may also be integrated in the study setting in order to achieve comprehensive results.

Author contribution

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

Ethical approval

The study was approved by Hacettepe University Non-interventional Clinical Research Ethical Committee (Project registration number GO-16/99 and decision number 16969557-337).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Evaluating the Correlation of Mortality and Biochemical Parameters in Community-acquired and Hospital-acquired Pneumonia

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ABSTRACT

Objective: The associations of inflammation and immunity of host lead to higher mortality in both community-acquired and hospital-acquired pneumonia patients. Therefore, several inflammatory and immunological biomarkers are essential for diagnosis, prognosis, and survival. Among these inflammatory markers, such as older age, and higher blood urea nitrogen, creatinine, procalcitonin and C-reactive protein, and lower albumin levels have been shown to have strong correlations with worse outcomes and high mortality, especially in community-acquired pneumonia patients. In this study, we investigated the correlation between several biochemical markers, which are mostly involved in inflammation, and mortality in not only community-acquired but also hospital-acquired pneumonia patients.

Material and Methods: This was a retrospective study of hospitalized community-acquired and hospital-acquired pneumonia patients in a third degree university hospital. In their initial blood tests (also used for diagnosis), blood urea nitrogen, creatinine, procalcitonin, C-reactive protein and albumin levels, and white blood cell, lymphocyte, neutrophil, platelet and erythrocyte counts, red blood cell distribution width and hemoglobin levels were measured. The outcome variable was mortality at 30 days. Statistical analysis included univariate comparisons of continuous variables between deceased and survivor groups, subject to mortality analysis and logistic regression in both community-acquired and hospital-acquired pneumonia patients.

Results: 272 hospitalized community-acquired and 80 hospital-acquired pneumonia patients were included. Patients who died during follow-up had older age and higher levels of procalcitonin, blood urea nitrogen, creatinine, and red blood cell distribution width in community-acquired pneumonia group. Remarkably, logistic regression analysis showed a significant relationship between creatinine and mortality, regardless of age, severity of community-acquired pneumonia and comorbidities. Creatinine is a strong independent prognostic factor, subject to mortality in community-acquired pneumonia group.

Conclusions: Older age, higher procalcitonin, blood urea nitrogen, creatinine and red blood cell distribution width levels are significant biomarkers for prediction of higher mortality in hospitalized community-acquired pneumonia patients.

Keywords: community-acquired pneumonia, hospital-acquired pneumonia, mortality, creatinine.

INTRODUCTION

Pneumonia is a common infectious disease that causes inflammation in the lung tissue and a major cause of mortality among infectious diseases globally. It is usually caused by various bacteria, viruses, and other microorganisms, and can lead to severe respiratory distress, hospitalization, and mortality. Mortality rates in pneumonia vary significantly based on the type of pneumonia, patient demographics, and pre-existing medical conditions, such as hypertension, diabetes mellitus, immune deficiencies, chronic kidney diseases or chronic obstructive pulmonary diseases [1]. Clinical scores, such as CURB-65 (confusion, urea, respiratory, blood pressure, >65 years)/ CRB-65 (confusion, respiratory, blood pressure) and pneumonia severity index (PSI) are used for indication of hospitalization, presence of severe complications and assessment of mortality. However, these scales have certain limitations, such as confusion assessment error, time consuming and expensive [2, 3]. Therefore, several biochemical (inflammatory and immunological) parameters have been studied in the context of community-acquired and hospital-acquired pneumonias, with the aim of identifying predictors of mortality and prognosis for improving patient outcomes [2, 4]. In this study, we aimed to serve additional evidence to the current literature on the effect of biochemical parameters on mortality in patients having community-acquired and hospital-acquired pneumonias.

Community-acquired Pneumonia (CAP)

CAP, the leading cause of death from infectious diseases worldwide, is a type of pneumonia that develops outside the hospital setting. It is a common respiratory illness and can lead to severe morbidity and mortality, especially in elderly patients or those with underlying health conditions. Various biochemical parameters have been studied in CAP, with the aim of identifying predictors of prognosis and mortality [2, 4] [3, 5].

C-reactive protein (CRP) is a biomarker of inflammation and is produced by the liver, in response to infections. CRP is elevated in bacterial as well as viral infections. Several studies have evaluated the role of CRP in predicting mortality in CAP. A study by Kruger et al. found that elevated levels of CRP (>150 mg/L) were associated with an increased risk of mortality in CAP patients [6]. Similarly, a study by Coelho et al. found that CRP levels were significantly higher in non-survivors of CAP, compared to survivors [7].

Procalcitonin (PCT) is another biomarker of infection that has been studied in the context of CAP. PCT is produced by various tissues and cells, including the thyroid gland and lungs, in response to bacterial infections. Since PCT is a blood marker for bacterial infections, PCT-guided therapy has proven to allow a significant reduction of duration and frequency of antibiotic therapy. A meta-analysis by Schuetz et al. found that PCT was a reliable predictor of mortality in CAP, with higher PCT levels being associated with increased mortality [8]. However, another study by Kutz et al. found that PCT levels were not significantly associated with mortality in CAP patients. In primary care and intensive care unit patients, no significant association of initial PCT levels and outcome was found [9].

Albumin is a protein synthesized by the liver and is involved in various physiological functions, including the regulation of osmotic pressure and the transport of various substances in the blood. Several studies have evaluated the role of albumin levels in predicting mortality in CAP. A study by Arnau-Barrés et al. found that low albumin levels were associated with increased mortality in CAP patients [10]. Similarly, a study by Eshwara et al. found that low albumin levels were an independent predictor of mortality in CAP patients [11]. Low albumin levels, ICU transfer and development of CAP-associated complications were found to be additional independent risk factors for prolonged length of hospital stay [12].

Additional biomarkers, such as prealbumin, Neutrophil Count Percentage (NCP) and Neutrophil/ Lymphocyte Ratio (NLR), pro-adrenomedullin (proADM) and pro-atrial natriuretic peptide (proANP), have been studied for predicting mortality in CAP. Serum Prealbumin Improves the Sensitivity of Pneumonia Severity Index in Predicting 30-day Mortality of CAP Patients [13]. NCP and NLR are promising candidate predictors of mortality for hospitalized CAP patients [5]. NLR improves the accuracy of PSI in predicting 30-day mortality of CAP patients [14]. NLR in adult CAP patients correlates with unfavorable clinical

outcomes [15]. In addition, proADM and proANP accurately predict short- and long-term all-cause mortality, prognosis and survival in CAP patients [16, 17].

Hospital-acquired Pneumonia (HAP)

Hospital-acquired pneumonia (HAP) is a type of pneumonia that develops in patients who are hospitalized for other medical conditions. It usually develops 48 hours after hospitalization and is not known to be in the incubation period at admission and defined as a pneumonia that occurs within 48 hours of hospital discharge. HAP is associated with significant morbidity and mortality, and is often caused by multi-drug-resistant organisms. Various biochemical parameters have been studied in HAP, with the aim of identifying predictors of mortality.

Procalcitonin (PCT) has been studied in the context of HAP, with the aim of differentiating between bacterial and non-bacterial causes of HAP. A meta-analysis by Liu et al. found that PCT was a reliable biomarker for differentiating between bacterial and non-bacterial causes of HAP, with higher PCT levels being associated with a higher likelihood of bacterial HAP [18]. However, the role of PCT in predicting mortality in HAP is less clear. A study by Yilmaz et al. found that PCT levels were not significantly associated with mortality in HAP patients [19].

MATERIALS AND METHODS

Patient evaluation

Inclusion criteria for our study were being above 18 years old and diagnosed with either CAP or HAP. Patients were grouped, according to diagnostic criteria for CAP and HAP in ATS/IDSA guidelines.

The diagnosis of CAP generally requires the demonstration of an opacity on chest imaging in a patient with a clinically compatible syndrome (eg, fever, dyspnea, cough, and sputum production), leukocytosis and elevations in creatinine and BUN levels [20].

HAP were diagnosed if two or more of the following clinical features are present: temperature greater than 38°C or less than 36°C; leukopenia or leukocytosis; purulent tracheal secretions and decreased partial pressure of oxygen in arterial blood [21].

Exclusion criteria for our study were being below 18 years old, pregnancy, having active infection except pneumonia, chronic kidney diseases, malignancies, connective tissue diseases and immunosuppressive treatment in a month.

In our study, patients were categorized, according to their gender, age, 30-day mortality (deceased or survivor), pneumonia type (community-acquired pneumonia vs hospital-acquired pneumonia), pneumonia evaluation score (for community-acquired pneumonia only) (CURB-65), cardiac additional disease (congestive heart failure and hypertension/coronary artery disease), neurological additional disease, and co-morbidities as COPD and DM.

This was a retrospective study of hospitalized CAP and HAP patients in a third degree university hospital. 272 community-acquired pneumonia patients and 80 hospital-acquired pneumonia patients who were followed up in the inpatient service in between January 2012 and December 2018 were included in the study, with the ethical approval of Ufuk University Ethical Committee (Approval No:12024861-10/12.01.2023). The 30-day mortality of the patients from the day of admission to the hospital were recorded. The patients were divided into two groups, according to their survival or death status.

In their initial blood tests which were obtained at admission, following parameters were studied: WBC numeric value (normal range 4.6-10.2 x103/µL), Hb (normal range 11.7-17 g/dL), RDW (10-17.6% normal range: under and above 15%), CRP value (normal range 0-0.5 mg/dL), PCT value (<0.5 ng/mL low risk, >2 ng/mL high risk), platelet value (normal range 142-450x10 3/µL), albumin value (normal range 3-5 mg/dL), BUN value (normal range 8-23 mg/dL), creatinine value (normal range 0.5-1.2 mg/dL). Location of abnormalities in chest x-ray (lobar vs multilobar) and specific chest x-ray radiological examination (consolidation, ground glass or consolidation and ground glass) were examined. All these parameters were evaluated in these patients having community-acquired or hospital-acquired pneumonia.

WBC counts were measured by fluorescent flow scatter. Hb was measured by sodium lauryl sulfate precipitation, RDW and platelet counts were measured by electric impedance.

Serum CRP levels were measured by nephelometric/turbidometric method (Beckman).

Serum PCT levels were measured by chemiluminescent magnetic particle separation assay (Beckman).

Serum albumin levels were measured by bromocresol based assay (Beckman).

Serum BUN levels were measured by an enzymatic (urease) method (Beckman).

Serum creatinine levels were measured by alkaline picrate based assay (Beckman).

Statistics

SPSS and R software were used for statistical analysis. The significance threshold was accepted as $p \leq 0.05$. Depending on parametric assumptions, continuous variables were given as mean ± SD or median as 1st and 3rd quartiles (descriptive statistics). Discontinuous variables were given as absolute frequency (n) and relative frequency (%). Univariate comparisons of continuous variables between groups subject to mortality analysis were performed with appropriate parametric or non-parametric tests (Student's t-test, Mann-Whitney U). When it was necessary to look at the correlations, the Spearman or Pearson correlation coefficients were used again according to whether the parametric assumptions are met or not. Simple logistic regression or Cox regression analyzes was performed to identify parameters that have independent effects on mortality (depending on assumptions and univariate results).

RESULTS

Demographic characteristics, comorbidities and laboratory test results were compared (Table 1, 2 and 3). The seven statistically significant results in univariate analysis (95% confidence interval) were: Age (mean 81.5 years old vs 72 years old, $p < 0.001$), CURB-65 score (mean 4 vs 3, $p < 0.001$), RDW (17.3% vs 16.05%, $p = 0.017$), CRP (73.1 mg/L vs 26.23 mg/L, $p=0.047$), PCT (1.51 ng/mL vs 0.44 ng/mL, $p=0.038$), BUN (47 mg/dL vs 26 mg/dL, $p < 0.001$) and creatinine (1.67 mg/dL vs 1 mg/dL, $p < 0.001$) in CAP cases with respect to mortality (Table 1).

Older age, high RDW and creatinine levels were significantly correlated with mortality in CAP in logistic regression analysis, respectively $p<0.001$, OR=1.078; $p=0.024$, OR=1.114; $p<0.001$, OR=1.691 (Table 2). Creatinine was found to be a very strong factor (Table 2). There was no statistical difference in univariate analysis of hospital-acquired pneumonia (Table 3).

DISCUSSION

Since, despite recent advances in antimicrobial treatment, CAP is still the leading cause of death from infectious diseases worldwide, the discovery of novel diagnostic and prognostic biomarkers, showing the expression of the host's inflammatory response against the pathogen microorganism, and host's immunity is essential for improving patient management in CAP. CRP, PCT, and several inflammatory cytokines, such as Interleukins (IL) IL-1 and 6 are the most frequently studied [2, 16].

In addition, HAP is also associated with significant morbidity and mortality, and is often caused by multi-drug-resistant organisms. Similarly, several diagnostic and prognostic biomarkers, such as PCT is studied in several studies to improve patient outcome and evaluate the risk of mortality [18].

CURB (confusion, uremia, abnormal respiratory rate and low blood pressure) is used to identify patients with CAP who may be candidates for outpatient vs. inpatient treatment. Because of the limitations in clinical scores, such as CURB or PSI, several studies evaluated the predictive role of various inflammatory and immunological biomarkers for predicting mortality and prognosis in pneumonia patients.

PCT can help guide the decision to initiate or discontinue antibiotic treatment in patients with established diagnoses of CAP [22]. Even though PCT is a good marker for the assessment of severity and mortality of CAP patients [23, 24], the combination of PCT and CURB-65 was more accurate than other prognostic models in predicting mortality [25]. Both IL-6 and PCT are significant for prediction of 30-day mortality in hospitalized patients with CAP [26]. PCT levels were positively correlated with PSI and CURB-65 scores [27]. In another study, PCT was not an independent predictor of 30-day mortality and its increased levels were correlated with pneumonia severity, but not CRP levels [28].

Table 1. Summary of community-acquired pneumonia cases with respect to mortality

	Deceased (n=48)	Survivors (n=224)	*p* value
Sex			
Male	29 (60.4%)	142 (63.4%)	0.699
Female	19 (39.6%)	82 (36.6%)	
Age (years, median (min-max))	81.5 (76-86)	72 (60-81)	**<0.001**
CURB-65 score	4 (3.5-4)	3 (3-3)	**<0.001**
Any comorbidity	35 (72.9%)	147 (65.6%)	0.330
Chronic heart failure	16 (33.3%)	53 (23.7%)	0.224
Hypertension or coronary artery disease	15 (31.3%)	73 (32.7%)	0.842
Any neurological comorbidity	6 (12.5%)	18 (8%)	0.478
Chronic obstructive pulmonary disease	12 (25%)	65 (29%)	0.575
Diabetes mellitus	6 (12.5%)	23 (10.3%)	0.844
White blood cell count (mm^3, median (min-max))	10.86 (7.8-16.2)	12.25 (8.17-16.09)	0.399
Low	6 (12.5%)	11 (4.9%)	0.141
Normal	16 (33.3%)	78 (34.8%)	
High	26 (54.2%)	135 (60.3%)	
Hemoglobin (g/dL, median (min-max))	13 (11-14)	12.65 (10.85-14)	0.514
Low	16 (33.3%)	86 (38.4%)	0.680
Normal	29 (60.4%)	129 (57.6%)	
High	3 (6.3%)	9 (4%)	
Red blood cell distribution width (%, median (min-max))	17.3 (15.35-18.9)	16.05 (14.05-18.3)	**0.017**
Low	0 (0%)	15 (6.7%)	0.057
Normal	24 (50%)	129 (57.6%)	
High	24 (50%)	80 (35.7%)	
<15	9 (18.8%)	83 (37.1%)	**0.015**
≥15	39 (81.3%)	141 (62.9%)	
C-reactive protein (mg/L, median (min-max))	73.1 (17.76-133.06)	26.23 (9.82-100.5)	0.047
Low	0 (0%)	0 (0%)	0.313
Normal	7 (14.6%)	47 (21%)	
High	41 (85.4%)	177 (79%)	
Procalcitonin (ng/mL, median (min-max))	1.51 (0.12-16.71)	0.44 (0.14-2.58)	**0.038**
Low	15 (31.3%)	95 (42.4%)	0.266
Normal	11 (22.9%)	52 (23.2%)	
High	22 (45.8%)	77 (34.4%)	
Platelet count (mm^3, median (min-max))	250 (164.5-327.5)	220 (162.5-295)	0.294
Low	10 (20.8%)	43 (19.2%)	0.950
Normal	34 (70.8%)	160 (71.4%)	
High	4 (8.3%)	21 (9.4%)	
Albumin (mg/dL, median (min-max))	2.75 (2.3-3.35)	2.9 (2.6-3.3)	0.127
Low	29 (60.4%)	122 (54.5%)	0.691
Normal	19 (39.6%)	101 (45.1%)	
High	0 (0%)	1 (0.4%)	
Urea (mg/dL, median (min-max))	47 (24.5-73.5)	26 (15-52.5)	**<0.001**
Low	0 (0%)	0 (0%)	0.003
Normal	14 (29.2%)	118 (52.7%)	
High	34 (70.8%)	106 (47.3%)	
Creatinine (mg/dL, median (min-max))	1.67 (1.19-2.34)	1 (0.7-1.38)	**<0.001**
Low	0 (0%)	26 (11.6%)	**<0.001**
Normal	12 (25%)	113 (50.4%)	
High	36 (75%)	85 (37.9%)	
Pulmonary involvement			
Lobar	26 (54.2%)	127 (56.7%)	0.748
Multilobar	22 (45.8%)	97 (43.3%)	
X-ray findings			
Consolidation	19 (39.6%)	126 (56.3%)	0.079
Ground-glass opacity	14 (29.2%)	55 (24.6%)	
Both	15 (31.3%)	43 (19.2%)	

Table 2. Parameters independently associated with mortality in patients with community-acquired pneumonia

	Beta coef.	Std. Error	Wald	p value	OR	95% CI for OR	
Age	0.075	0.018	18.304	**<0.001**	**1.078**	1.042	1.116
RDW	0.108	0.048	5.115	**0.024**	**1.114**	1.014	1.223
Creatinine	0.525	0.151	12.113	**0.001**	**1.691**	1.258	2.273
Constant	-9.875	1.763	31.383	<0.001	0	–	–

OR: odds ratio, CI: confidence interval, RDW: red blood cell distribution width.

Final step (#3) of the backward stepwise method is shown. Variables included in the model (step #1): Age, RDW, procalcitonin, urea, creatinine. Hosmer and Lemeshow statistic: 0.979, Nagelkerke R2: 0.249.

In addition, CRP and PCT support the diagnosis of pneumonia and help distinguish bacterial from viral causes of CAP, but studies have found that these tests reliably add no value to the initial clinical and radiographic evaluation [29]. The reported sensitivity and specificity of CRP for pneumonia both range from approximately 40 to 90 percent and vary substantially with the cutoff value used [30-36]. Similarly, the reported sensitivity for procalcitonin ranges widely from 38 to 91 percent [20]. Elevated CRP values cannot support a diagnosis of bacterial infection when the illness has lasted less than 7 days, but may indicate a complication of viral infection after a week [37].

Overall, CRP, WBC counts and ILs are non-specific for diagnosing pneumonia, besides PCT may not be effective to distinguish between bacterial versus viral infections, only can used for monitoring response to antimicrobial therapy. Additionally, increased procalcitonin concentrations were shown following surgery, trauma, and in systemic viral infections [22].

Among these biochemical markers, as we described in details in the introduction, elevated serum creatinine level was reported as an independent predictor of in–hospital mortality in severe CAP patients [38], similar to our study. This study created a novel clinical model named CLCGH scoring system, including serum creatinine>259.5μmol/L, WBC>17.35×109/L, CRP>189.4μg/mL, Glasgow Coma Scale ≤9 and serum bicarbonate ≤17.65mmol/L and each index was an independent factor for hospital mortality in severe CAP [38]. In another study, serum creatinine levels above the 1.1 mg/dL and blood urea nitrogen levels above 21 mg/dL were associated with an increased risk of mortality in univariate analysis [39]. Similar to our study, Sloane et al. reported that 20% rise in serum creatinine level above baseline was associated with 30–days mortality in CAP patients [3, 40].

Besides, in a recent study, arrival serum markers, such as BUN, albumin, creatinine, BUN/albumin ratio and BUN/creatinine ratio, were correlated with the incidence of mortality during hospitalization. When survivors and non-survivors were compared, creatinine >/= 2.8 mg/dL showed the highest odds (OR = 7.656, 95% CI = 2.281-25.692; p = 0.001); followed by CURB-65 score >/= 4 (OR = 4.958, 95% CI = 0.418-58.784; p = 0.266); and BUN >/= 24.7 mg/dL (OR = 3.364, 95% CI = 1.033-10.954; p = 0.062). Similar to our study, serum creatinine was a fair predictor of in-hospital mortality (AUC = 0.721) showed 53.0% sensitivity and 87.0% specificity at cut-off 2.8 mg/dL. Among five serum markers, increased serum creatinine was a better predictor of in-hospital mortality in adults having CAP [3].

As it is known, using creatinine as a biomarker in CAP patients is limited due to the comorbidities, such as chronic kidney disease, which we excluded in our study. Initial increased creatinine (>1.5 mg/dL) levels were found to be not a risk factor for early mortality, but a risk factor for pulmonary complications, so alterations in renal function tests should be evaluated [41].

In our study, we found that in addition to older age, higher CURB-65 score, BUN, creatinine, RDW, CRP and PCT levels were statistically significant in CAP cases, with respect to mortality (Table 1). Similar to the study of Adnan et al, serum creatinine levels were an independent strongest predictor of mortality in CAP patients (Table 2). Creatinine was found to be a very strong factor (Table 2), but it is important to keep in mind that creatinine is a parameter that acts in a very narrow range and easily differs, because of the comorbidities.

We could not find any significant difference between survivors and deceased in HAP patients. Similar to our study, Yilmaz et al. could not find any significant biomarkers in HAP patients [19]. We have 80 HAP patients in our study, compared to 272

Table 3. Summary of hospital-acquired pneumonia cases with respect to mortality

	Deceased (n=17)	Survivors (n=63)	*p value*
Sex			
Male	11 (64.7%)	41 (65.1%)	1.000
Female	6 (35.3%)	22 (34.9%)	
Age (years, median (min-max))	80 (73-85)	75 (68-81)	0.111
Any comorbidity	14 (82.4%)	57 (90.5%)	0.611
Chronic heart failure	5 (29.4%)	24 (38.1%)	0.706
Hypertension or coronary artery disease	10 (58.8%)	33 (52.4%)	0.842
Any neurological comorbidity	6 (35.3%)	17 (27%)	0.711
Chronic obstructive pulmonary disease	11 (64.7%)	46 (73%)	0.711
Diabetes mellitus	4 (23.5%)	13 (20.6%)	1.000
White blood cell count (mm^3, median (min-max))	12.9 (10.6-15.6)	14.7 (11.2-19.7)	0.108
Low	0 (0%)	0 (0%)	
Normal	4 (23.5%)	12 (19%)	0.682
High	13 (76.5%)	51 (81%)	
Hemoglobin (g/dL, median (min-max))	11.5 (10.5-12.8)	11.9 (9.81-14.1)	0.764
Low	10 (58.8%)	33 (52.4%)	
Normal	6 (35.3%)	25 (39.7%)	0.885
High	1 (5.9%)	5 (7.9%)	
Red blood cell distribution width (%, median (min-max))	17.9 (16.8-18.8)	18.2 (16.8-20.1)	0.414
Low	0 (0%)	0 (0%)	
Normal	7 (41.2%)	17 (27%)	0.257
High	10 (58.8%)	46 (73%)	
<15	1 (5.9%)	5 (7.9%)	1.000
≥15	16 (94.1%)	58 (92.1%)	
C-reactive protein (mg/L, median (min-max))	7.71 (4.54-16.52)	10.29 (5-18.8)	0.480
Low	0 (0%)	0 (0%)	
Normal	6 (35.3%)	18 (28.6%)	0.591
High	11 (64.7%)	45 (71.4%)	
Procalcitonin (ng/mL, median (min-max))	0.63 (0.27-4.9)	0.48 (0.24-2.31)	0.720
Low	6 (35.3%)	33 (52.4%)	
Normal	6 (35.3%)	16 (25.4%)	0.456
High	5 (29.4%)	14 (22.2%)	
Platelet count (mm^3, median (min-max))	220 (142-288)	220 (153-282)	0.906
Low	4 (23.5%)	12 (19%)	
Normal	12 (70.6%)	46 (73%)	0.896
High	1 (5.9%)	5 (7.9%)	
Albumin (mg/dL, median (min-max))	3.1 (2.8-3.2)	3 (2.7-3.6)	0.625
Low	6 (35.3%)	26 (41.3%)	
Normal	11 (64.7%)	37 (58.7%)	0.655
High	0 (0%)	0 (0%)	
Urea (mg/dL, median (min-max))	34 (20-52)	26 (19-37)	0.203
Low	0 (0%)	0 (0%)	
Normal	5 (29.4%)	28 (44.4%)	0.401
High	12 (70.6%)	35 (55.6%)	
Creatinine (mg/dL, median (min-max))	0.78 (0.64-1.12)	0.78 (0.65-1.04)	0.676
Low	0 (0%)	0 (0%)	
Normal	12 (70.6%)	52 (82.5%)	0.274
High	5 (29.4%)	11 (17.5%)	
Pulmonary involvement			
Lobar	10 (58.8%)	24 (38.1%)	0.208
Multilobar	7 (41.2%)	39 (61.9%)	
X-ray findings			
Consolidation	6 (35.3%)	18 (28.6%)	
Ground-glass opacity	3 (17.6%)	7 (11.1%)	0.586
Both	8 (47.1%)	38 (60.3%)	

CAP patients. The difference between survivors and deceased in HAP patients can be significant with a larger sample size.

We could not evaluate 90-day mortality in the survivor group, since most of the patients have been discharged from hospital before 90 days and unfortunately, we could not reach that information. With a larger sample size, we believe that we can evaluate 90-day mortality.

In this study, we aimed to serve additional evidence to the current literature on the effect of biochemical parameters on mortality in patients having CAP and HAP. Even though we found seven parameters strongly significant and in addition, creatinine as an independent strongest predictor of mortality in CAP patients, we believe that with a relatively larger patient size, we will get new biochemical biomarkers that are more significant in both CAP and HAP patients, with respect to mortality for patient management. We can use these biomarkers independently or with pneumonia severity assessment scales, in order to prevent the risk of complications and mortality, especially in CAP patients.

Author contribution

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

Ethical approval

The study was approved by the Ufuk University Ethical Committee (Approval No:12024861-10/12.01.2023).

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

A Case of Widespread Keratosis Pilaris-like eruption Associated with Nilotinib Used for Chronic Myelogenous Leukemia

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ABSTRACT

Keratosis pilaris is a skin disorder which is characterized by follicular hyperkeratosis. It is most commonly seen in patients with atopic dermatitis and ichthyosis vulgaris. Abnormal keratinization of the hair follicle leads to plugging and bumpy, rough appearance. Upper extensor arms, thighs, buttocks and cheeks are most commonly affected by the disease. Even though keratosis pilaris is associated with autosomal dominant inheritance; it may also be seen as a side effect of various targeted cancer therapies including BRAF and tyrosine kinase inhibitors. Herein, we would like to present a case of keratosis pilaris that had developed secondary to nilotinib treatment.

Keywords: Keratosis pilaris, nilotinib, tyrosine kinase inhibitors.

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INTRODUCTION

Nilotinib is a second-generation tyrosine kinase inhibitor used for the treatment of Philadelphia chromosome-positive chronic myeloid leukemia (CML) [1]. It results in quick and efficacious response, especially when used in patients with CML [2]. Just like other chemotherapeutic agents, nilotinib is reported to be associated with various cutaneous side effects including pruritus, xerosis, rash, alopecia and eyebrow thinning [3,4]. Herein, we would like to report a case of widespread keratosis pilaris observed in a patient receiving nilotinib for CML.

CASE PRESENTATION

A 27-year old man receiving treatment for CML was admitted to our clinic, due to the emergence of widespread, pinpoint, follicular papules involving the trunk and extremities. He was diagnosed with BCR-ABL1 positive CML in 2018 and he was takingoral 300 mg nilotinib twice a day for 1 year. The patient was not underany other treatment and there was no familial or personal history of atopy. The papules appeared in an eruptive manner within the first 3 months of nilotinib therapy. Dermatological examination showed erythematous, brownish follicular, pinpoint papules on a slightly hyperpigmented background involving the chest and upper extremities (Figure 1). No other side effects related to the eyebrows, scalp hair and hair belonging to the other body parts were detected. The lesions were clinically compatible with keratosis pilaris, therefore the patient is diagnosed with keratosis pilaris like eruption secondary to nilotinib. He was reassured of the benign nature of the lesions and started on 10% urea ointment thrice daily. The itch and xerosis

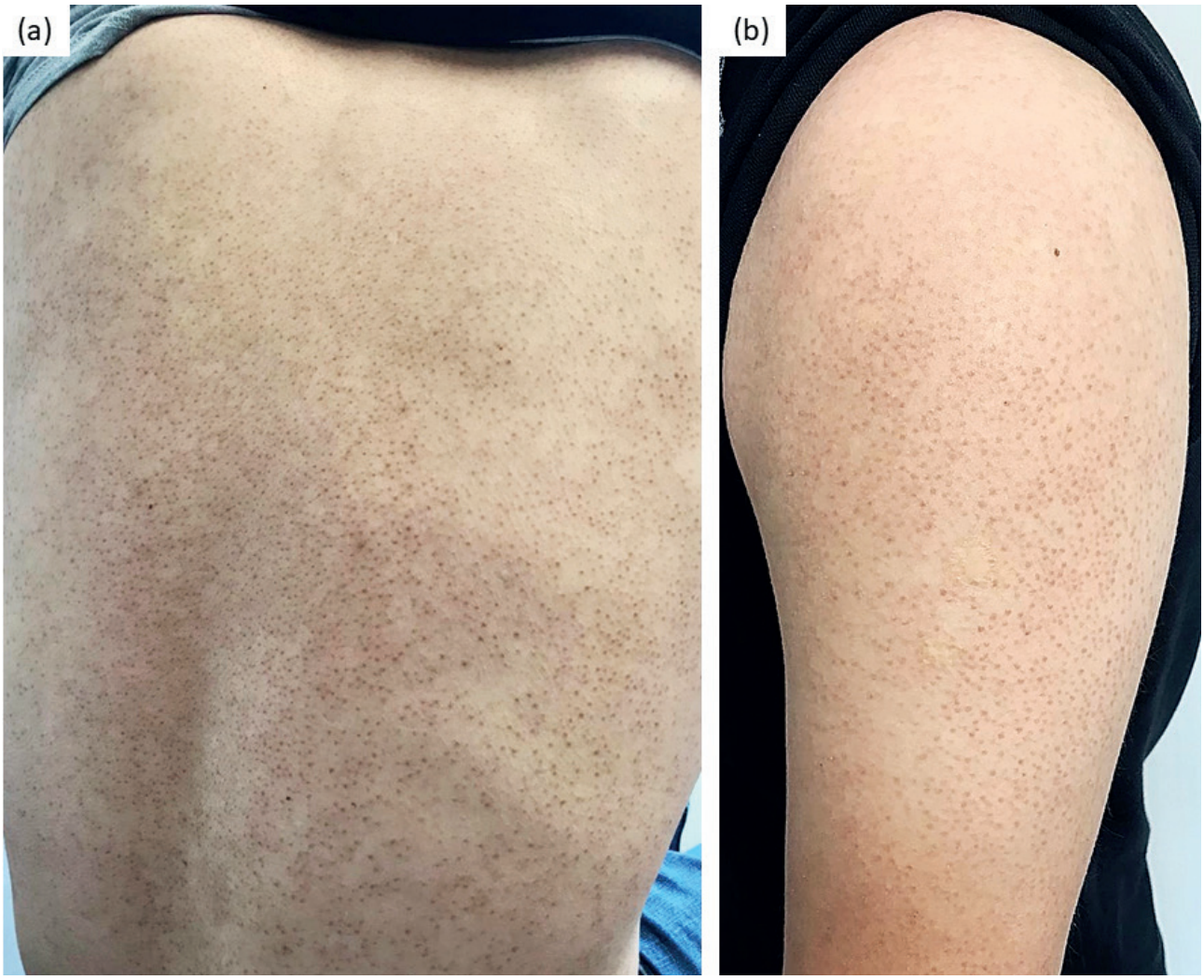

Figure 1. Black/erythematous, folliculocentric papules on a slightly hyperpigmented skin are present on the back (a) and the lateral upper arms (b)

associated with keratosis pilaris were relieved by the application of 10% urea ointment within two months without side effects. Since keratosis pilaris developing in the setting of nilotinib use, tends to have a benign clinical course and the patient was relieved by the topical treatment, nilotinib was continued.

DISCUSSION

Various chemotherapeutic agents have been associated with cutaneous side effects. In a review by Amitay-Laish et al. [4], it is emphasized that tyrosine kinase inhibitors imatinib, dasatinib and nilotinib are commonly associated with various cutaneous side effects including maculopapular rash, hypo/hyperpigmentation, lichenoid reactions, urticaria, alopecia, pruritus and dry skin. Keratosis pilaris is a common cutaneous disorder characterized by brown/black folliculocentric, pinpoint papules most commonly observed on the lateral aspects of the upper and lower extremities [5]. The possible differential diagnoses of keratosis pilaris, are lichen spinulosus, lichen nitidus, folliculitis and Darier disease [6]. Keratosis pilaris is associated with xerosis, atopic dermatitis and ichthyosis vulgaris. In our patient, there was no prior history of any skin disease; and lesions compatible with keratosis pilaris had showed up three months after the initiation of nilotinib treatment. Similar to our patient, Leong et al. [7] reported a case of nilotinib-induced keratosis pilaris in patient with CML. Distinctively, in the aforementioned case, keratosis pilaris had manifested 3 days after the initiation of nilotinib treatment which is quite a short time interval compared to our case (three months). In another letter by Shimizu et al. [8] multiple keratotic papules appeared on the trunk and extremities of a CML patient six months after the start of

nilotinib. Although the exact mechanism is not fully determined, C-kit, which is targeted by tyrosine kinase inhibitors, is also shown to be expressed not only in tumor cells but also in basal layers of the skin and melanocytes [9]. So, interfering with c-kit might have resulted in the emergence of the associated cutaneous adverse events. Since keratosis pilaris associated with nilotinib use is self-limited and tends to follow a benign course, symptomatic treatment with emollients and keratolytic agents is enough, interruption of nilotinib is usually not necessary.

CONCLUSION

In conclusion, by reporting a case of nilotinib-induced keratosis pilaris, we wanted to raise awareness of the cutaneous side effects of tyrosine kinase inhibitors. Proper management of keratosis pilaris with keratolytic agents and humectants must be initiated promptly to increase compliance to the treatment.

Author contribution

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

Ethical approval

Informed consent for publication of medical images was taken from the patient.

Funding

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

High-grade Atrioventricular Block Due to Lacosamide and Tizanidine Combination Therapy for Epilepsy and Multiple Sclerosis

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ABSTRACT

Drug-induced atrioventricular (AV) block can be caused by cardiac and non-cardiac medications. The clinical condition may be temporary, persistent, or recurrent. However, there is no standard approach for management and follow-up of patients with drug-induced AV block. Herein, we presented a patient with the diagnosis of epilepsy and multiple sclerosis who admitted to emergency room with epileptic seizure. Temporary advanced AV block was observed on admission and during in-hospital follow-up which was thought to be caused by lacosamide and tizanidine medications and improved after drug discontinuation.

Keywords: Lacosamide, tizanidine, atrioventricular block

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INTRODUCTION

High-grade atrioventricular (AV) heart block is characterized by complete dissociation of the electrical activity of the atrium and ventricle that can manifest in different settings with varying symptomatology and severity [1]. Although the escape rhythm can mostly compensate it from the distal part of the block, severe and life-threatening consequences like syncope and death may occur. Among several causes, drug-induced AV block can be observed either in the recommended dose, overdose, or a combination of responsible drugs that may require temporary or permanent pacing. Drug-induced AV block can be transient, persistent, or recurrent [2]. However, there was scarce data about the monitorization, management, and follow-up strategy of drug-induced AV block patients after an index event. Herein, we presented our approach to a patient admitted to our emergency room with a high-grade AV block due to lacosamide and tizanidine medications.

CASE

A 51-year-old female patient was admitted to our emergency room with a sudden-onset epileptic seizure. Past medical history revealed the diagnosis of epilepsy and multiple sclerosis for four years. She has been regularly taking medications of acetylsalicylic acid 1x300 mg, tizanidine 2x6 mg, lacosamide 2x200 mg, levetiracetam 2x1500 mg, and baclofen 1x10 mg. There was no suspicion of a drug overdose. Physical examination, including vital signs, was unremarkable except for a pulse rate of 40 bpm. 12-lead electrocardiography (ECG) on admission showed a complete AV block (ventricular rate of 33 bpm) (Figure 1A). Laboratory test results, including electrolytes, were within normal reference limits. A bedside emergent echocardiography indicated normal findings. Defibrillator patches with a cutaneous temporary pacing ability (back-up rate of 40 bpm) were applied and closely followed in the emergency room. However, spontaneous sinus rhythm was observed after one hour of admission (ventricular rate of 76 bpm) (Figure 1B). The Naranjo Algorithm,

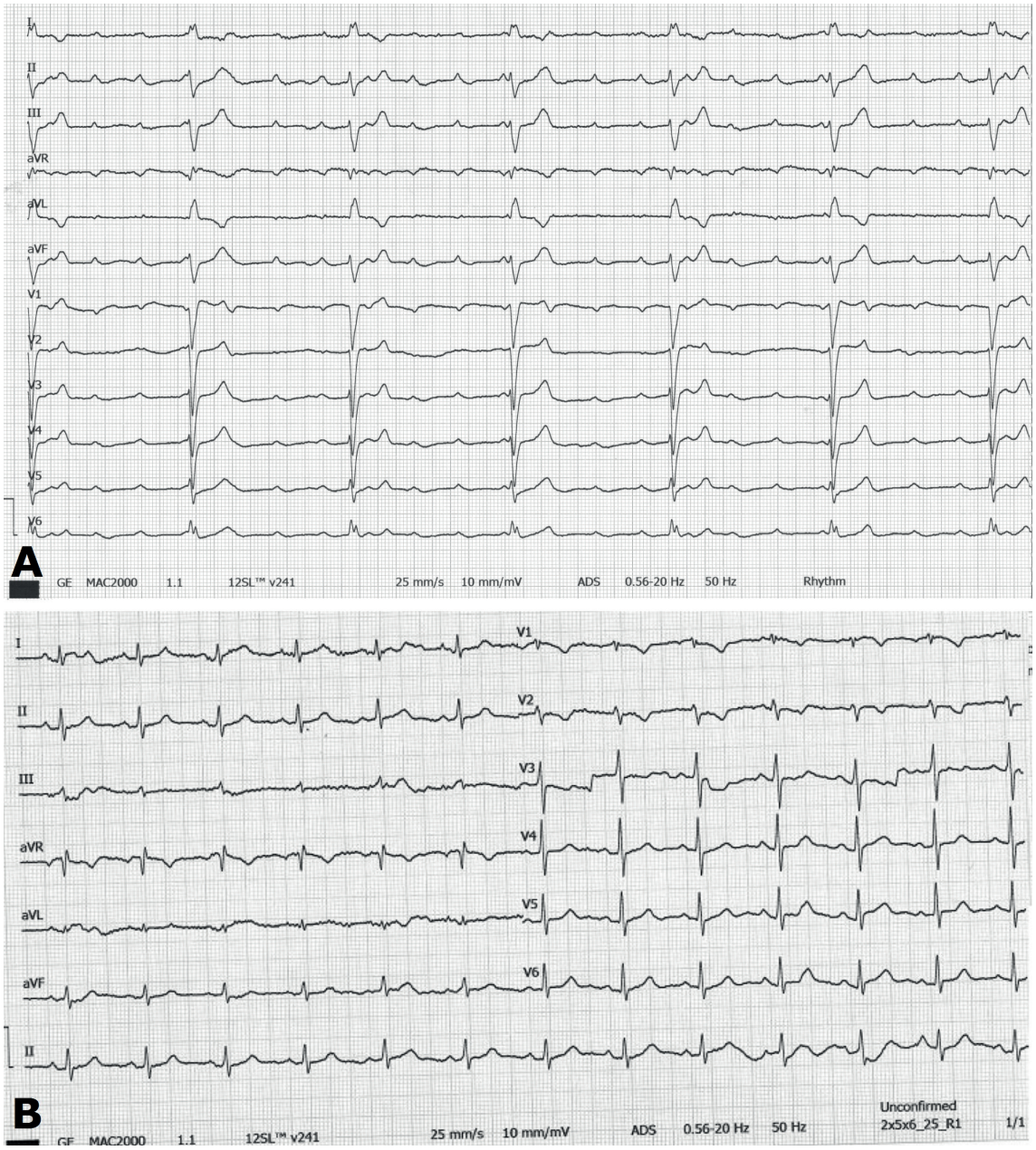

Figure 1. A) 12-lead electrocardiography of the patient on admission to the emergency room was consistent with complete AV block. B) Spontaneous sinus rhythm was observed after one-hour of admission.

or Adverse Drug Reaction Probability Scale [3] total score was calculated as 7 for our patients which proposed that there was a probable adverse drug reaction for those suspected drugs of "lacosamide and tizanidine". Because of previously published case reports, *tizanidine* was stopped immediately. *Lacosamide* was also replaced with valproic acid after an electroencephalography (EEG) test after a neurology consultation. She closely monitored and followed for the recurrence of seizures. However, the patient developed Mobitz type 2 second-degree AV block with a ventricular rate of 45 bpm at the 22nd hour of follow-up (Figure 2A). The patient returned to spontaneous sinus rhythm (ventricular rate of 97 bpm) after 10 minutes of a close monitorization (Figure 2B). After a 48-hours duration of hospitalization and monitoring for heart rhythm, she was discharged uneventfully. A 48-hour Holter monitorization at the 7th-day control visit showed no bradyarrhythmia.

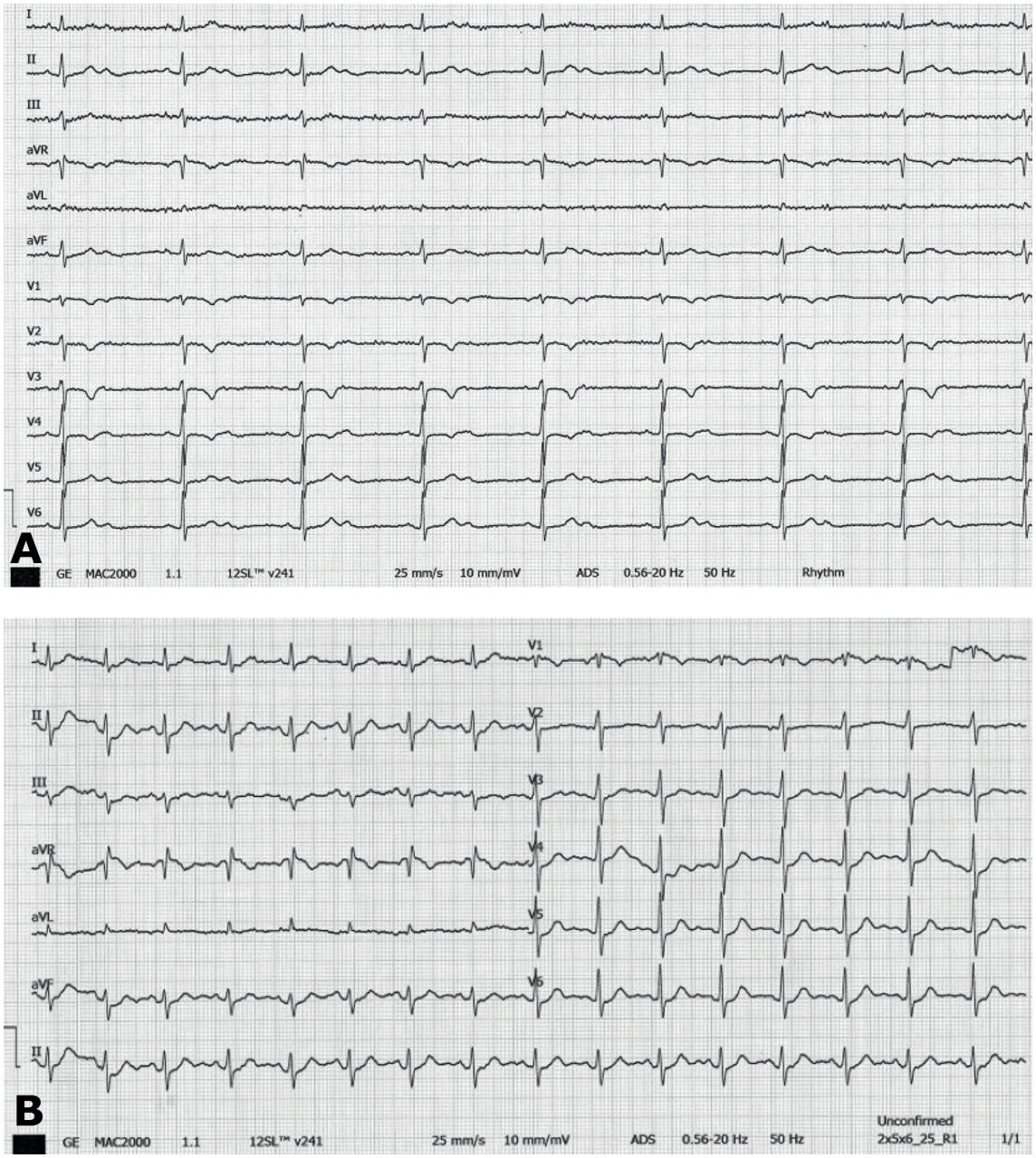

Figure 2. A) The patient developed Mobitz type 2 second-degree AV block with a ventricular rate of 45 bpm at the 22nd hour of follow-up. B) The patient returned to spontaneous sinus rhythm after 10 minutes of a close monitorization.

DISCUSSION

Transient or persistent advanced second-degree and third-degree AV block may occur in various clinical situations like acute myocardial infarction, and electrolyte imbalance such as hyperkalemia and after radiofrequency catheter ablation. It may be life-threatening if the underlying cause is not resolved. Drugs, including beta-blockers, calcium channel blocking agents, digoxin, and antiarrhythmic drugs, are the leading causes. Still, on the other hand, AV block may occur related to medications that are not used for their cardiac effects like antiepileptic drugs. Elderly patients are more often on polypharmacy and have more extensive comorbidity, and this population has more structural heart disease and conduction abnormalities. These conditions increase the risk of adverse drug effects through drug-drug or drug-disease interactions and abnormal pharmacokinetics [4]. A significant percentage of all these reactions involve the cardiovascular system, the most frequent drug-related cardiovascular abnormality, is probably bradycardia [5].

Drug-induced AV block is potentially reversible but inadequately characterized by bradyarrhythmia reason [6]. It is not known if patients can expect a benign course after cessation of the responsible drug. In a common clinical approach, drug-induced advanced AV block can be reversible with drug discontinuation, and patients who are symptomatic or hemodynamically unstable require temporary pacing. The long-term prognosis remains unclear. Moreover, it is little known what proportion of patients have a recurrence and need permanent pacemaker implantation.

In our case, the patient had a history of using lacosamide and tizanidine. Lacosamide (LCM) is developed for use as an antiepileptic drug. It is currently indicated as an adjunctive treatment for partial-onset seizures in adults with focal epilepsy, especially in patients who are unresponsive to conventional therapies. Off-label use is seen in status epilepticus. LCM is eliminated primarily by the kidneys (elimination half-life 15-23 hours) and can be used orally and intravenously with a maximum daily dose of 400 mg, typically divided twice daily [7,8] LCM is associated with dose-dependent PR interval prolongation which can result from AV nodal or infra-Hisian conduction delay due to its effect on voltage-gated sodium channels. However, action potential generation in the AV node is mediated through voltage-gated Ca2+ channels, with the sodium current playing a minimal role. Potential LCM effects on calcium currents or autonomic tone may result in direct AV nodal effects causing varying degrees of atrioventricular block [9]. Sinus bradycardia and ventricular tachycardia may also occur. Adverse cardiac effects are more severe with overdose than in the therapeutic dose range and mainly seen during the titration period [10]. Lachuer et al.[11] reported that an 88-year-old female patient with hypertension and angina developed 3rd-degree AV block after taking the only initial dose of lacosamide. Furthermore, Stamm et al.[12] reported a case of second-degree AV block occurring within hours after intravenous lacosamide and improvement after withdrawal of the drug in a healthy, athletic young adult who had baseline bradycardia with no known cardiac comorbidities. Tizanidine is also used as a muscle relaxant and acts centrally to agonize a-2 autoreceptors (elimination half-life 2-4 hours) [13]. It can cause dizziness, hypotension, and severe bradycardia. Cortes et al.[13] reported a case of a 93-year-old female patient that developed profound hypotension and bradycardia that require permanent pacing after a single dose of tizanidine. In our case, there was no suspicion of a drug overdose, and 3rd-degree AV block was seen in the therapeutic dose range. The patient was using lacosamide and tizanidine for three years in the same dosage. It was evident from previous reports that these drugs might cause bradyarrhythmia or AV block in the therapeutic range. However, the essential triggering factor for advanced AV block in our patient was unclear. We thought that epileptic seizure itself might modulate autonomic nerve activity [14,15] and AV conduction might be inhibited by epileptic origin in the brain like temporal lobe seizures [16]. Furthermore, using lacosamide and tizanidine medications probably facilitated the impact of epileptic seizure via autonomic modulation on AV conduction. However, recurrence of AV block at 22nd hour of follow-up without recurrence of epileptic seizure confirmed the dominant impact of lacosamide and tizanidine medications on AV block. Thus, we diagnosed the patient as drug-induced AV block.

Furthermore, there is no standard approach to the management of patients with drug-induced AV block. This situation seems to be benign and thought to be reversible with drug cessation. However, recurrences can be seen during follow-up, and some patients need permanent pacemaker implantation [17]. If possible, offending medications should be discontinued. At this point, the patient's indication for drug use and whether there are alternative medicines are essential. Additional factors, such as underlying AV conduction abnormalities, may facilitate drug-induced AV block development. So considering all these factors, an individual decision must be made for each patient. Therefore, the LCM was replaced with valproic acid, and tizanidine was discontinued in our patient in whom no recurrence of AV block was observed at early follow-up.

Author contribution

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

Ethical approval

N/A as the paper was a case report

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Conflict of interest

The authors declare that there is no conflict of interest.

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