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Instructions to Authors

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The journal aims to publish papers of general interest relating to advances in medical practice and novel treatments that will be of interest to general practitioners, medical students, and senior practitioners and specialists. Marmara Medical Journal also aims to publish all types of research conducted by medical students.

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ii. Walker M, Hull A. Preterm labor and birth. In: Taeusch HW, Ballard RA, eds. Avery's Diseases of the Newborn. Philadelphia: WB Saunders, 1998: 144,153.

iii. Hagström H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017; 67: 1265-73. doi: 10.1016/j.jhep.2017.07.027.

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Physical activity in the treatment of primary insomnia

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ABSTRACT
Insomnia is commonplace in the general population. Poor sleep quality leads to various health dysfunctions and compromises the well-being of the affected individuals. Non-pharmacologic approaches should be considered the first-line treatment as suggested by various guidelines. Among others (e.g., sleep hygiene, cognitive-behavioral therapy, light therapy), appropriate physical activity seems to be promising in treating and preventing sleep disturbance development. We found that improvement in a particular objective and subjective sleep quality parameters may be attributed to appropriate physical activity. When further analyzing the activity, light-intensity aerobic exercises and resistance training reduced insomnia symptoms. High-intensity interval training also showed a positive effect on the improvement in depressive symptoms. Regarding mind-body practices, current evidence is insufficient to conclude. However, it was documented that stress, depression, and anxiety reduction, can improve well-being.
Keywords: Exercise, Insomnia, Physical activity, Sleep quality

1. INTRODUCTION

Insomnia is characterized by difficulty falling asleep, interrupted sleep, and/or early awakening. The International Classification of Sleep Disorders, 3rd edition (ICSD 3) divides insomnia into acute and chronic (> three months, at least three times a week) [1]. The prevalence of sleep induction or retention disorders is estimated at 30% – 48% [2]. Good sleep quality is associated with better performance, physical and psychological well-being [3]. Primary insomnia cannot be attributed to an existing medical, psychiatric, or environmental cause. Psychological symptoms such as irritability, anxiety, and depression are more common in people with insomnia. A decreased concentration, less productivity, and poorer health are also observed [4]. Conversely, sleep disturbances may result in various dysfunctions, e.g., hypertension [5], weakened immunity [6], cognitive decline [7], and other different health problems [8].

In light of the potential side effects of commonly used sleep-promoting medications, increased attention is paid to non-pharmacologic approaches [9]. One of the promising non-pharmacologic approaches to improving sleep quality is physical exercise [10]. WHO guidelines address regular physical activity as an indisputable part of a ´healthy lifestyle´. It may improve health in patients presenting with various chronic disorders, such as obesity, cardiovascular diseases, diabetes, cancer, anxiety, and depression [11]. Physical activity can also contribute to the maintenance of physical and mental well-being [12]. Despite the variety of proven and potential health benefits of exercise, the ´pandemic of physical inactivity´ has become a reality as a consequence of a sedentary lifestyle. A recent meta-analysis by Li and coworkers, including 23 trials with 1269 patients who received exercise therapy, reported a significant effect on the treatment of primary insomnia [13].

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Sleep and exercise show a mutual relationship in terms of sleep quality and physical performance. Various descriptions of how regular exercise influences sleep comprise effects on endocrine, metabolic and immune systems, and thermoregulatory changes [14]. Recently, awareness has been paid to exercise-related hippocampal neurogenesis. During this process, new neurons are born to be integrated into the hippocampus. One of the essential molecules mediating this process is known as the brain-derived neurotrophic factor (BDNF) [15]. This morphological and functional plasticity theory may provide a better insight into how physical activity can promote brain function. Erickson and colleagues, in their study, reported positive effects of aerobic exercise on increased hippocampal volume and cognitive function improvement, e.g., enhanced spatial memory after seven weeks of an aerobic exercise program [16]. Notably, exercise-related hippocampal neurogenesis might contribute to better understanding the antidepressant effects of exercise. In summary, physical activity exerts various neurochemical changes positively affecting well-being and the ability to cope with stressful encounters, e.g., due to the transient increase of cortisol and plasma β-endorphin levels [17, 18]. This review aims to discuss current literature regarding different types of physical activities/exercises in relation to sleep quality.

2. PHYSICAL ACTIVITIES

Physical activity-based treatment approaches and protocols

Physical activity can be defined as any bodily motion produced by the action of skeletal muscles that expends energy and can be performed in the way of transportation, as part of work, housework, leisure activities, or when participating in exercise or sports [11]. Exercise as a component of physical activity is usually planned, structured, and repetitive. It can further be characterized by its type, duration, frequency, and intensity. Regarding the intensity of physical activity, metabolic equivalents (METs) are commonly used in epidemiological research to assign an intensity category to a specific physical activity. One MET can be defined as an energy cost while sitting quietly (resting metabolic rate) and is equivalent to a caloric consumption of 1kcal/kg/hour. Guidelines from the American College of Sports Medicine and the American Heart Association recommend using the following reference thresholds: 1.5 to 3.0 METs for light, 3.0 to 6.0 METs for moderate, and >6.0 METs for vigorous intensities. Concerning an individual's cardiorespiratory fitness, a commonly used measure is a scale of 0–10, where 0 is sitting, and 10 represents the highest level of effort possible [19]. Being aware of simplification and potential overlap, we categorized different physical activities according to their types and intensities.

Exercise to prevent and treat insomnia

The role of physical activity in insomnia treatment

Light intensity physical activities do not substantially raise heart or breathing rates and energy expenditure. These may include, e.g., walking, pilates, or stretching exercises. Hartescu et al. conducted a randomized controlled trial (RCT) in a sample of inactive people with insomnia, exploring the effect of brisk walking on self-reported outcomes. At six months post-baseline, the authors reported that the increased physical activity group significantly reduced insomnia symptoms compared to the control group, where participants maintained their lifestyle as usual [20]. Chen and colleagues, in their systematic review with meta-analysis from 2020, documented an improvement in sleep quality in individuals practicing pilates-based exercised. On the other hand, the effect on reducing the use of sleep-promoting medications was not supported by evidence according to their study [21]. Two RCTs documented the beneficial effects of pilates on sleep quality [22, 23]. Pa and coworkers conducted a study exploring the effects on reducing sleep difficulties in older adults with cognitive decline and sleep complaints. According to their results, a combination of light cognitive exercises together with light-intensity activities, such as stretching, was reported to be superior to moderate or high-intensity workouts [24].

Resistance training increases strength without significantly changing peak oxygen consumption [25]. Exemplary activities would be, e.g., weight-lifting, body-weight workouts, or resistance band exercises. In their systematic review from 2018, Kovacevic and coworkers made an effort to determine both the acute and chronic effects of resistance training on sleep characteristics. According to their findings, regular resistance training improved sleep quality, with further benefits of combining with aerobic exercise. As regards the acute effects of resistance exercise on sleep quality, the evidence was inconsistent [26]. In their RCT, D'Aurea et al. compared the effects of stretching (group 1) and resistance exercise (group 2) on chronic insomnia. Both exercise types were similarly effective in improving subjective and objective sleep parameters, while both approaches were found superior to the control group (group 3) [27]. A combination of resistance training, walking, and social activity for seven weeks improved sleep in older adults more than in a regular care control group. It also showed no significant same-day effects of resistance training on sleep architecture [28].

High-intensity interval training (HIIT) is a cardiovascular exercise defined by short bursts of repeated vigorous activity that consists of short periods of rest or low-intensity exercise for body recovery. Jurado-Fascoli et al., in their RCT, observed improved objective sleep quality parameters, like total sleep time, sleep efficiency, and sleep interruptions after 12 weeks of HIIT training [29]. In their community-based study, Bullock and coauthors found HIIT inferior for improving sleep in insomniacs compared with moderate-intensity or stretching exercises. HIIT after eight weeks of training showed a positive effect on the improvement in depressive symptoms, sleep quality, and cardiorespiratory adaptation [30]. A study with middle-aged men showed that practicing HIIT close to bedtime reduced sleep quality in the first three hours [31].

Aerobic exercise is a moderate-intensity physical activity associated with cardiovascular conditioning. It can include activities like jogging, hiking, or dancing. Reid KJ et al. randomized individuals older than 55 years to either group

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with aerobic physical exercise or control group with no physical activity. After 16 weeks of the training program, the authors assessed the study participants for sleep problems. This study concluded that subjects in the active group improved their sleep quality, efficiency, latency, duration, and daytime dysfunction. This group also showed less symptoms of depression, sleeping during the day, and increased vitality [32]. Ezati and colleagues did not find a positive effect of 4 weeks of aerobic exercise on sleep duration among university students. However, eight weeks of training positively affected all components of sleep [33]. Another relevant RCT showed that moderate-intensity aerobic exercise in patients with chronic primary insomnia decreased presleep anxiety and increases sleep [34]. A RTC by Hartescu with colleagues showed that more than 150 min of moderate – to vigorous-intensity physical activity per week for six months decreased severe insomnia symptoms [35]. Two studies documented that moderate-intensity exercise 90 minutes before bed by young and healthy men did not negatively impact sleep quality [36, 37].

Mind-body exercises have also been studied for the treatment of sleep disturbances. Notably, the mechanisms for improving sleep quality are different.

Yoga, in its traditional ancient Indian conception, is more way of living, also consisting of nutrition, lifestyle advices, and meditation. The Western version, sometimes called 'postural yoga' is a form of mind-body exercise. There are various yoga styles, e.g., Hatha, Vinyasa, Bikram, Ashtanga, Acroyoga, and many others, [38] with various intensities [39]. Postural yoga consists of changing static and dynamic positions with a specific breathing pattern. Concerning yoga practice in women with sleep problems, Wang and coauthors documented an improvement in sleep quality [40]. In their systematic review, Crammer and colleagues reported moderate evidence for yoga practice-related short-term effects on relieving symptoms of depression [41]. Yoga has also been documented to be beneficial in improving sleep quality in the elderly (aged ≥ 60 years) [42], patients with malignancy [43], and in postmenopausal women [44]. As reported by Innes and Selfe, yoga may improve in older women with restless legs syndrome [45]. On the other hand, European guidelines for the diagnosis and treatment of insomnia do not recommend yoga to treat insomnia because of poor evidence [46]. Regarding possible adverse effects of yoga, musculoskeletal injuries were reported, mainly when practicing without supervision [47]. In their systematic review with meta-analysis from 2019, Tang and coworkers concluded walking to be superior to yoga in reducing sleep disturbance in cancer patients [48]. In 2019, Kreutz and colleagues compared RCTs reporting sleep outcomes of patients after breast cancer treatment, following different mind-body and physical exercises. They included 22 studies with 2107 participants and reported improved subjective sleep outcomes after both physical and mind-body exercises. On the other hand, a positive impact on objective sleep measures was not documented [49].

Tai Chi, a mind-body exercise rooted in traditional Chinese martial art, is nowadays popular in Western society. Tai Chi exercise can vary from low to moderate intensities and can also be suitable for middle-aged or older individuals [50]. Tai chi is widely used as a complementary treatment for different conditions. A favorable impact of Tai chi has also been documented on psychological well-being, including reduced stress and depression [51]. As reported in two recent systematic reviews with meta-analyses, Tai Chi exercise may positively affect sleep quality [52, 53]. Concerning possible adverse effects of meditative movement therapies, short term symptoms of anxiety may be reported initially [54].

Future Perspectives

A matter of debate is the potential harming effect of exercising before bedtime. According to sleep hygiene, [55] exercise close to bedtime is not recommended. Regarding vigorous exercise, a systematic review and meta-analysis conducted by Stutz et al. support this recommendation [56]. However, their review does not support the hypothesis that evening exercise, in general, has a negative impact on sleep quality. To this end, it seems that one should evaluate the appropriateness of evening exercise case by case.

Conclusions

The exercise intervention represents a safe and widely accessible health-promoting activity. In addition to various physical and mental benefits, regular exercise seems to be a good alternative treatment option to improve sleep quality. There is no optimal general recommendation as regards a specific physical activity type. Every individual should perform activities/exercises that fit in their lifestyle and preferences.

Compliance with Ethical Standards

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Infections in ANCA-associated vasculitis and lupus nephritis treated with rituximab

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ABSTRACT

Objective: Patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) and systemic lupus erythematosus (SLE) are prone to infections. This study aims to clarify infectious complications in terms of both the disease and the specific treatments used.

Patients and Methods: Sixty-three patients with SLE and AAV with kidney involvement treated with rituximab or cyclophosphamide were included. Patients were examined regarding infections, comorbidities, immunosuppressives, estimated glomerular filtration rate (eGFR), use of prophylactic antibiotics, hospitalization, and death.

Results: Patients with SLE experienced more genitourinary infections in general (p=0.009). In the rituximab group, SLE patients had a higher incidence of genitourinary infections, septicemia, and intensive care unit admissions. Furthermore, lupus patients with serious infections were all treated with rituximab and had a higher incidence of low respiratory tract infections (p=0.003). On the contrary, treatment with rituximab did not cause an increased risk of infection among AAV patients compared to cyclophosphamide. In general, patients with serious infections had lower IgG and total Ig levels (p<0.05).

Conclusion: Patients with SLE had a higher risk of genitourinary infections and also a higher risk of sepsis, serious infections, and hospitalizations when treated with rituximab. Immunoglobulin levels are associated with serious infections.

Keywords: ANCA-associated vasculitis, Immunoglobulin, Infections, Lupus nephritis, Rituximab.

1. INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is an autoimmune disease characterized by necrotizing vasculitis which affects small to medium-sized blood vessels. AAV is a group of diseases that is subgrouped clinically and pathologically as granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA, formerly known as Churg-Strauss syndrome). Glomerulonephritis can be seen in about 60% of cases, whereas sepsis is the leading cause of mortality [1]. Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease that affects the connective tissue [2]. Renal involvement, also referred to as lupus nephritis, is a significant organ involvement that occurs in around 30-50% of cases. Infections are one of the leading causes of mortality in the first five years [3].

Rituximab (RTX) is a monoclonal anti-CD20 antibody that depletes CD20+ B cells for up to 24 weeks. RTX or cyclophosphamide (CYC) is recommended with glucocorticoids for remission-induction in organ or life-threatening AAV [4]. Likewise, RTX or CYC can also be considered for the management of organ-threatening or refractory disease in SLE [5, 6]. Even before RTX treatment, infection was a significant cause of mortality with standard therapies including CYC and glucocorticoids (GC) for lupus nephritis and AAV [7, 8]. With the introduction of RTX, infection rates were initially expected to be lower than with standard therapies; however, this proved to be false with the adverse events being similar to CYC in the RITUXVAS and RAVE trials [9, 10]. Specifically, hypogammaglobulinemia can be observed after rituximab treatment due to the depletion of B cells, which raises concerns for infections associated with RTX [11].

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Patients with AAV and SLE have high mortality and morbidity rates both due to the underlying disease as well as the therapies used. In the current study, we examined infectious complications in AAV with glomerulonephritis and lupus nephritis patients treated with RTX or CYC using a retrospective data analysis. Consequently, we sought to clarify infectious complications in terms of both the disease and the specific treatments used.

2. PATIENTS and METHODS

We conducted a single-center retrospective study of patients with AAV and lupus nephritis followed in the Nephrology and Rheumatology Outpatient Clinics of Marmara University Hospital. The study was approved by the Marmara University School of Medicine Clinical Research Ethics Committee (06.09.2019 approval number: 09.2019.393).

Patients

Systemic lupus erythematosus and AAV patients with kidney involvement were included in the study. All patients received at least one infusion of CYC or RTX for induction or maintenance of remission between September 2002 and May 2019. Follow-up data were obtained from local hospital records or the national database. Patients who received immunosuppressive therapy for other causes, or who had a history of renal transplantation, or malignancy were excluded from the study.

Clinical Data

The following data were collected from medical records: age, gender, smoking and alcohol status, comorbidities, disease type, date of diagnosis, date of RTX/CYC administrations, cumulative doses of glucocorticoids, rituximab, cyclophosphamide, and other immunosuppressives, follow-up duration after immunosuppressive administration, estimated glomerular filtration rate (eGFR) use of prophylactic antibiotics against pneumocystis jirovecii (PJP), number of infections, type of infections (opportunistic, severe, viral, or bacterial), administration of antibiotics, antiviral and antifungal medications, hospitalization and death due to infections. The Modification of Diet in Renal Disease (MDRD) formula was used to calculate the estimated glomerular filtration rate (eGFR) with the creatinine obtained from the last blood analysis. Severe infections were defined as infectious events requiring parenteral treatment, hospitalization, intensive care unit (ICU) admission, and/or death. In addition, pretreatment and posttreatment immunoglobulin levels were recorded, if available.

Statistical Analysis

Statistical analyses were performed with SPSS (IBM SPSS Statistics for Windows, v. 25.0. Armonk, NY: IBM Corp). Data were expressed as mean ± standard deviation (for normally distributed data) or median and interquartile range (IQR, for data that were in skewed distribution) for continuous variables, and as number (%) for categorical variables, as applicable. The chi-square test was used to compare categorical variables, while the Mann-Whitney or t-test was used to compare continuous variables. A p-value below 0.05 was considered statistically significant in all analyses.

3. RESULTS

Patient characteristics

Sixty-three patients were included in the study (36 female, 27 male). Results were compared between both the disease groups (SLE vs. AAV) and the immunosuppressive drugs (RTX vs. CYC).

Twenty-two SLE patients (19 (86.4%) females), and 41 AAV patients (17 (41.5%) females) were included in the study (p<0.001). The median duration of follow-up was 26.4 ± 21.3 months for the whole group of patients. SLE patients were younger (33.5 ± 11.7 vs 55.8 ± 11.8 years, p<0.001) and the mean eGFR was higher (73.8 ± 51.7 vs 45.6 ± 35.7 ml/min, p=0.013). Patient characteristics are summarized in Table I.

Table I. Patient characteristics and infections

Features	All patients (n:63)	SLE (n:22)	AAV (n:41)	P
Female gender, n (%)	36 (57.1)	19 (86.4)	17 (41.5)	**0.001**
Age, year	48 ± 15.8	33.5 ± 11.7	55.8 ± 11.8	**<0.001**
Follow-up (months)	26.4± 21.3	32.7 ± 25.1	23.1 ± 18.4	0.089
Smoker, n (%)	25 (39.7)	5 (22.7)	20 (48.8)	**0.044**
DM, n (%)	6 (9.5)	0	6 (14.6)	0.059
HT, n (%)	45 (71.4)	15 (68.2)	30 (73.2)	0.676
COPD, n (%)	4 (6.3)	0	4 (9.8)	0.13
ASCVD, n (%)	10 (15.9)	3 (13.6)	7 (17.1)	0.722
CKD, n (%)	27 (42.9)	7 (31.8)	20 (48.8)	0.195
AZA treatment, n (%)	41 (65.1)	12 (54.5)	29 (70.7)	0.199
CsA treatment, n (%)	4 (6.3)	4 (18.2)	0	**0.005**
MMF treatment, n (%)	15 (23.8)	14 (63.6)	1 (2.4)	**<0.001**
TMP-SMX prophylaxis, n (%)	14 (22.2)	0	14 (34.1)	**0.002**
Cumulative steroid (MP), gram	12.2 ± 6.3	14.3 ± 6.7	11.1 ± 5.8	**0.049**
eGFR, ml/min/1,73 m2	55.5± 43.8	73.8 ± 51.7	45.6 ± 35.7	**0.013**
All infections, n (%)	59 (93.7)	22 (100)	37 (90.2)	0.13
LRTI, n (%)	21 (33.3)	5 (22.7)	16 (39)	0.19
GUTI, n (%)	21 (33.3)	10 (45.5)	9 (22)	**0.009**
Sepsis, n (%)	10 (15.9)	**4 (18.2)**	6 (14.6)	0.71
SI, n (%)	17 (27)	6 (27.3)	11 (26.8)	0.97
Death, n (%)	7 (11.1)	2 (9.1)	5 (12.2)	0.71

AAV: ANCA-associated vasculitis, ASCVD: Atherosclerotic cardiovascular disease, AZA: Azathioprine, CKD: Chronic Kidney Disease, COPD: Chronic, obstructive pulmonary disease, CsA:Cyclosporin A, DM: Diabetes Mellitus, eGFR: Estimated Glomerular Filtration rate, GUTI: Genitourinary Tract Infections, HT: Hypertension, LRTI: Lower respiratory tract infections, MMF: Mycophenolate mofetil, MP: Methylprednisolone, SI: Serious Infections, SLE: Systemic Lupus Erythematosus, TMP-SMX: Trimethoprim-sulfamethoxazole

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SLE versus AAV Patients According to Immunosuppressive Drugs

Systemic lupus erythematosus patients experienced more genitourinary infections than AAV patients independent from immunosuppressive treatment (p=0.009) and no other difference was detected in terms of infectious diseases and treatments (Table I). However, when we examined the disease groups according to immunosuppressive drugs, there were important differences. In the RTX group, SLE patients were younger, predominately female, used more cyclosporine and mycophenolate mofetil, and had less prophylactic antibiotic usage. They also had a higher incidence of genitourinary infections, septicemia, and intensive care unit admissions than AAV patients (Table II). In the CYC group, SLE patients were also younger, predominantly female, used more mycophenolate mofetil, and used fewer prophylactic antibiotics than AAV patients. However, in the CYC group, AAV patients had a lower estimated glomerular filtration rate at the last hospital visit and were prone to lower respiratory tract infections (LRTI) and hospitalizations (Table III).

Table II. SLE vs. AAV in the RTX treatment group

Variables	SLE RTX (n:12)	AAV RTX (n:25)	P
Age, year, mean±SD	35 ± 12.3	54 ± 13.9	<0.001
Female gender, n (%)	10 (83.4)	10 (40)	0.013
CsA treatment, n (%)	2 (16.7)	0	0.036
MMF treatment , n (%)	8 (66.7)	1 (4)	<0.001
TMP-SMX prophylaxis, n (%)	0	7 (28)	0.042
GUTI, n (%)	8 (66.7)	7 (28)	0.025
Sepsis, n (%)	4 (33.3)	2 (8)	0.05
ICU admission, n (%)	4 (33.3)	2 (8)	0.05

AAV: ANCA-associated vasculitis, CsA:Cyclosporine A, GUTI: Genitourinary Tract Infections, ICU: Intensive Care Unit, MMF: Mycophenolate mofetil, RTX: Rituximab, SLE: Systemic Lupus Erythematosus, TMP-SMX: Trimethoprim-sulfamethoxazole

Table III. SLE vs. AAV in the CYC treatment group.

Variables	SLE CYC (n:10)	AAV CYC (n:16)	P
Age, year	31.8 ± 11.5	58 ± 7.2	0.001
Female gender, n (%)	9 (90)	7 (43.8)	0.018
Smoker, n (%)	0 (0)	8 (50)	0.007
AZA treatment, n (%)	5 (50)	14 (87.5)	0.036
MMF treatment, n (%)	6 (60)	0 (0)	<0.001
TMP-SMX prophylaxis, n (%)	0 (0)	7 (43.8)	0.014
LRTI, n (%)	1 (10)	8 (50)	0.037
Hospital admission, n (%)	0 (0)	5 (31.3)	0.049
eGFR, ml/min/1,73 m2	62.95 ± 35.4	35.6 ± 28.8	0.042

AAV: ANCA-associated vasculitis, AZA: Azathioprine, CYC: Cyclophosphamide, eGFR: Estimated Glomerular Filtration rate, LRTI: Lower respiratory tract infections, MMF: Mycophenolate mofetil, SLE: Systemic Lupus Erythematosus, TMP-SMX: Trimethoprim-sulfamethoxazole

RTX versus CYC According to Disease

We compared RTX and CYC in both lupus and AAV patients individually. In SLE patients, the RTX group had a higher proportion of smokers and a shorter duration of follow-up after the last immunosuppressive infusion. The RTX group also had a higher incidence of septicemia, hospitalization, serious infections, and admission to ICU units (Table IV). We did not identify any statistical difference between RTX and CYC groups in AAV patients in terms of patient characteristics and/or infectious side effects.

Table IV. RTX versus CYC in SLE patients

Variables	RTX SLE (n:12)	CYC SLE (n:10)	P
Smoker, n (%)	5 (41)	0	0.02
Follow-up (months)	190 ± 143	320 ± 88	<0.0001
Sepsis, n (%)	4 (33)	0	0.044
SI, n (%)	6 (50)	0	0.009
Hospital admission, n (%)	6 (50)	0	0.009
ICU admission, n (%)	4 (33)	0	0.044

CsA:Cyclosporin A, CYC: Cyclophosphamide, ICU: Intensive Care Unit, SI: Serious Infections, SLE: Systemic Lupus Erythematosus, TMP-SMX: Trimethoprim-sulfamethoxazole

Serious Infections

At least one serious infection episode occurred in 17 (27%) of all patients. In terms of patient characteristics, disease type (SLE or AAV), immunosuppressive therapy type (RTX or CYC), the cumulative dosage of immunosuppressive therapies, and prophylactic antibiotic use, there were no statistically significant differences between patients who had serious infections and those who did not. Patients who had serious infections needed more antibiotic and antiviral treatment, as expected. Moreover, these patients had lower IgG and total Ig levels and consequently received more immunoglobulin replacement therapy (Table V).

Table V. *Serious infections (SI)*

Variables	SI (+) (n:17)	SI (-) (n:46)	P
LRTI, n (%)	12 (70)	9 (19.6)	<0.0001
Bacterial infections, n (%)	17 (100)	33 (71.7)	0.014
Fungal infections, n (%)	6 (35.2)	6 (13)	0.046
Antibiotic treatment, n (%)	17 (100)	31 (74)	0.007
Antiviral treatment, n (%)	8 (47)	6 (13)	0.004
IVIG treatment, n (%)	4 (23.5)	1 (2.2)	0.005
IgG, g/L	6.2 ± 2.1	8.5 ± 2.5	0.026
Total Ig, g/L	7.97 ± 2.6	10.98 ±3.2	0.023

IVIG: Intravenous immunoglobulin, LRTI: Lower respiratory tract infections, SI: Serious Infections

Six of the 22 SLE (27%) patients had serious infections and all patients with serious infection episodes had been treated with RTX. These patients also had lower IgG levels than those

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without serious infections. Patients with serious infections had more LRTI (Table VI).

Table VI. *Serious infections in SLE patients*

Variables	SI (+) (n:6)	SI (-) (n:16)	P
RTX treatment, n (%)	6/0 (100)	6/10 (37.5)	0.009
URTI, n (%)	1 (16.7)	11 (68.75)	0.029
LRTI, n (%)	4 (66.7)	1 (6.3)	0.003
IgG, g/L	5.96 ± 2.33	10.2 ± 2.9	0.047
Total Ig, g/L	8.2 ± 3.2	13.4 ± 3.5	0.053

LRTI: Lower respiratory tract infections, MMF: Mycophenolate mofetil, RTX: Rituximab, SLE: Systemic Lupus Erythematosus, TMP-SMX: Trimethoprim-sulfamethoxazole, URTI: Upper respiratory tract infections

Eleven of 41 AAV (27%) patients had serious infections. Patients with serious infections had more LRTI, skin infections, and fungal infections. These patients required additional antibiotic, antiviral, and antifungal treatment, as well as immunoglobulin replacement therapy. Moreover, the eGFR values of these patients were lower (Table VII).

Table VII. *Serious infections in AAV patients*

Variables	SI (+) (n:11)	SI (-) (n:30)	P
IS cumulative dosage, gram	2.6 ± 1.65	7.5 ± 5.1	0.004
Follow-up (months)	307 ± 244	834 ± 568	0.005
Total infection number	4.91 ± 2.8	2.83 ± 3.1	0.059
LRTI, n (%)	8 (72.8)	8(26.7)	0.007
Skin infection, n (%)	7 (63.6)	9 (30)	0.05
Fungal infection, n (%)	5 (45.5)	1 (3.3)	0.001
Antibiotic treatment, n (%)	11 (100)	20 (66.6)	0.028
Antiviral treatment, n (%)	6 (54.5)	4 (13.3)	0.006
Antifungal treatment, n (%)	4 (36.3)	1 (3.3)	0.004
IVIG treatment, n (%)	2 (18.2)	0 (0)	0.017
eGFR, ml/min/1.73 m2	27 ± 31	52 ± 35	0.046

AAV: ANCA-associated vasculitis, eGFR: Estimated Glomerular Filtration rate, IS: Immunosuppressive, IVIG: Intravenous immunoglobulin, LRTI: Lower respiratory tract infections, SI: Serious infection

4. DISCUSSION

Systemic lupus erythematosus and AAV patients had comparable rates of general infectious episodes, except genitourinary infections, which were more prevalent in SLE patients, regardless of immunosuppressive treatments used. The increased prevalence of genitourinary infections in SLE patients may be related to their younger age and female predominance. It is known that the prevalence of genitourinary infections is increased in SLE patients [12, 13]. Furthermore, we compared the effects of RTX in SLE and AAV patients. We found that SLE patients had a higher risk of genitourinary infections, septicemia, and admissions to the intensive care unit. Higher prescriptions of prophylactic antibiotics in AAV patients may be associated with less sepsis and intensive care unit admissions rates. Kronbichler et al., reported a reduction in serious infections in AAV patients who received prophylactic trimethoprim/sulfamethoxazole (TMP-SMX) with RTX infusions [14]. TMP-SMX prophylaxis effectively reduces the incidence of PJP in patients receiving RTX infusions, with mild adverse effects [15].

When assessing the cyclophosphamide treatment, we identified that 50% of AAV patients had LRTI and that 31.3% of AAV patients were hospitalized, which was greater than the 10% LRTI prevalence among SLE patients. Older age and a longer smoking history may contribute to a higher risk of LRTI and hospitalization among AAV patients, despite the increased use of prophylactic antibiotics. Charlier et al., reported that 16% of GPA patients had bronchopulmonary infections in their study [16]. In addition, Goupil et al., observed that 39% of AAV patients receiving cyclophosphamide were hospitalized due to infections, with 50% of these hospitalizations linked to LRTI [17]. The hospitalization rates of these studies were comparable to ours. However, there was no mention of smoking history in these investigations. In their six-month follow-up trial, Ginzler et al., found one LRTI infection (1.2%), among 83 SLE patients receiving cyclophosphamide induction and mycophenolate mofetil remission treatment [18]. In our study, only one (10%) of the lupus nephritis patients treated with cyclophosphamide and followed for thirty months had LRTI. Contreras et al., found 10.2% LRTI with cyclophosphamide induction and mycophenolate mofetil/azathioprine remission therapy in their study of 39 individuals with lupus nephritis [19]. However, the small number of lupus patients in our study must be considered.

Despite a shorter follow-up period, RTX-treated SLE patients presented with a higher incidence of sepsis, severe infections, hospitalizations, and ICU admissions than CYC-treated SLE patients (Table IV). During follow-up, two lupus patients died of an infection following rituximab infusions, whereas no lupus patients died following cyclophosphamide infusions. However, statistically, the mortality rates were insignificant due to the small number of patients. A recent meta-analysis of rituximab in 392 patients with lupus nephritis reported four sepsis and three infection-related deaths [20]. When we evaluate patients with serious infections and hospital admissions, patient selection with comorbidities may lead to differences between our study and earlier research. These results suggest that lupus patients with other comorbidities should be closely monitored for infections during and after rituximab treatments. In AAV patients, we did not find any significant difference between CYC and RTX use concerning sepsis, serious infections, hospitalizations, or ICU admissions. Previous reports support our findings [10, 21-23].

We also examined serious infections. Lupus patients with serious infections had a higher incidence of LRTI and were all treated with RTX. Total Ig and IgG levels were also lower in SLE patients with serious infections. Likewise, AAV patients had more LRTI as well as fungal infections whereas immunoglobulin levels were similar in patients with and without serious infections. However, more immunoglobulin replacement therapy was administered to patients with serious infections in this patient group. Interestingly, patients with serious infections had lower eGFR levels at the last hospital visit. Thus, serious infections

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may deteriorate renal functions in the long term. We also found significant correlations between immunoglobulin levels and serious illness. Patients with serious infections had a higher number of LRTI and their mean IgG and total Ig levels were lower. It is known that both CYC and RTX therapies are associated with hypogammaglobulinemia [24]. Hypogammaglobulinemia does not necessarily cause infections, but it raises the probability of infection [25]. In their study of 177 patients with autoimmune disorders, Marco et al., found that 34% of patients developed IgG hypogammaglobulinemia after rituximab treatment, and 3% of patients required immunoglobulin replacement therapy. However, they did not detect a correlation between serious infections and IgG levels [26]. Besada et al., showed in AAV patients that immunoglobulin levels were lower in patients with serious infections and decreased levels of immunoglobulin after the first infusion was an independent risk factor for serious infections [27]. Currently, EULAR/ERA-EDTA guidelines published in 2016 recommend regular immunoglobulin screening for patients with recurrent infections following immunosuppressive treatment [4].

Our study has several limitations. Most importantly, our patient number was small. However, lupus nephritis and ANCA-associated vasculitis are both infrequent diseases. Secondly, the study was retrospective, and patients with inadequate follow-up data had to be excluded.

In conclusion, we evaluated infections in AAV and SLE patients. Patients with lupus nephritis had a higher risk of genitourinary infections in general, as well as a higher risk of sepsis, serious infections, and hospitalizations when treated with rituximab. On the contrary, treatment with RTX did not cause an increased risk of infection among AAV patients as compared to CYC. Since, immunoglobulin levels seem to be associated with serious infections, we also recommend measuring immunoglobulin levels regularly and administering immunoglobulin replacement therapy when needed. Large-scale, long-term cohort studies are needed to better define serious infections and associated risk factors in AAV and SLE patients.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University School of Medicine Clinical Research Ethics Committee (06.09.2019 approval number: 09.2019.393). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Conflict of interest: The authors declare that they have no potential conflict of interest regarding the investigation, authorship, and/or publication of this article.

Author contributions: SGT, EA: Conception, Design, Fundings, Data Collection, Analysis and Interpretation, Literature Review, Writing – original draft, DBA, FAO, AV, IHA: Materials, Data Processing, ZST, RHD, EA: Supervision, Critical Review. All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The predictive value of HCT-CI and CCI comorbidity indices in predicting survival and mortality before allogeneic stem cell transplantation in acute leukemia patients: A single-centre experience

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ABSTRACT

Objective: Acute leukemia often involves comorbidities, impacting treatment decisions and patient outcomes. Clinicians commonly use the Charlson Comorbidity Index (CCI) and the Hematopoietic Stem Cell Transplantation Comorbidity Index (HCT-CI) to assess their influence. However, their effectiveness in predicting survival and non-relapse mortality (NRM) in acute leukemia patients under 65 undergoing allogeneic stem cell transplantation remains unclear.

Patients and Methods: We conducted a retrospective single-center analysis on adults diagnosed with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL). The study included 35 patients, comprising 16 AML and 19 ALL cases. Patients were categorized based on age-adjusted HCT-CI and CCI scores.

Results: The 2-year NRM rate was determined to be 51.4%. Statistical analysis found no significant associations between age-adjusted CCI (p=0.217) and age-adjusted HCT-CI (p=0.102) with NRM. However, median overall survival significantly varied based on risk levels (p=0.003), HCT-CI groups (p=0.009), and CCI groups (p=0.011).

Conclusion: Using age-adjusted HCT-CI and CCI for comorbidity scoring in initial assessment of acute leukemia patients and those under 65 shows promise. However, these indices were ineffective in predicting NRM, emphasizing the importance of considering other significant pre-transplant factors like genetic risk, conditioning regimens, and donor type.

Keywords: HCT-CI, CCI, Score, Allogeneic stem cell transplantation, Age adjusted, Acute leukemia

1. INTRODUCTION

Conditions that occur concurrently with acute leukemia significantly impact treatment planning and outcomes. Various indices are employed to assess how different comorbidities affect the primary disease and guide treatment strategies. The Charlson Comorbidity Index (CCI) and Hematopoietic Stem Cell Transplantation Comorbidity Index (HCT-CI) are commonly utilized for this purpose. When evaluated before allogeneic hematopoietic stem cell transplantation (Allo-HSCT), these indices not only determine the patient's suitability for Allo-HSCT but also aid in predicting post-transplant survival [1, 2].

The CCI, a standardized score calculated as just a simple weighted sum of comorbidity item scores, was developed in 1987 by Mary E. Charlson, and has been considered the gold-standard tool in clinical research as a prognostic index to predict mortality. The original version of the CCI was based on 19 items corresponding to different clinical comorbidities [3, 4]. These 19 selected conditions are weighted and totalled to an index on a scale of 0–37 points [5, 6] (Table I). Subsequently, different versions of the CCI have been developed based on different sources of data, including the age-adjusted CCI, ICD-9 code based CCI and ICD-10 code based CCI [7, 8].

The HCT-CI was initially designed using clinical data from 1055 consecutive patients treated with allogeneic HCT from 1997 to 2004 at the Seattle Cancer Care Alliance (SCCA)/ Fred Hutchinson Cancer Research Center (FHCRC) [9]. The index was validated among patients who underwent transplantation at the SCCA/FHCRC, [10] as well as other transplant institutions world-wide [11, 12]. The HCT-CI includes 17 pre-transplant comorbidities assigned a weighted semi-quantitative impact on outcomes based on the predictive hazard ratio (HR) for non-relapse mortality (NRM). The HCT-CI has been recently developed to help estimate the

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risk of NRM in two years after transplantation, based on pre-transplant comorbid diagnoses and objective evidence of organ dysfunction [9]. The HCT-CI is assessed on a scale of 0 to 29 [13] (Table II). In retrospective studies, the HCT-CI appears useful in non-myeloablative and myeloablative transplant recipients [14], in patients with acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) [15], lymphoma [12], or chronic lymphocytic leukemia [16], and in patients from more than one institution [10].

The CCI was initially designed to predict survival following different treatments in cancer patients and those with severe chronic conditions, but it was not originally intended for HSCT recipients. Moreover, the HCT-CI is an adapted iteration of the original CCI developed to assess how patients' comorbidities affect their post-transplant outcomes. There is no study in the literature that evaluates the performance of these indices in predicting survival and NRM in patients diagnosed with acute leukemia, under the age of 65, and undergoing allogeneic hematopoietic stem cell transplantation. The aim of this study was to assess the predictive performance of age-adjusted CCI and age-adjusted HCT-CI in these patients.

Table I. *Age-adjusted Charlson Comorbidity Index*

Comorbid condition	Weight
Age	<50 years **0** 50–59 years **1** 60–69 years **2** 70–79 years **3** ≥80 years **4**
Myocardial infarction (MI) History of definite or probable MI (EKG changes and/or enzyme changes)	**1**
Congestive heart failure Exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents	**1**
Peripheral vascular disease	**1**
Cerebrovascular accident or transient ischemic attack History of a cerebrovascular accident with minor or no residua and transient ischemic attacks	**1**
Dementia	**1**
Chronic obstructive pulmonary disease	**1**
Rheumatologic disease	**1**
Peptic ulcer Any history of treatment for ulcer disease or history of ulcer bleeding	**1**
Hemiplegia/ paraplegia	**2**
Diabetes mellitus	*Uncomplicated* ***1*** *End-organ damage* ***2***
Liver disease Mild: Chronic hepatitis (or cirrhosis without portal hypertension), moderate = cirrhosis and portal hypertension but no variceal, bleeding history, severe = cirrhosis and portal hypertension with variceal bleeding History	Mild **1** Moderate to severe **3**
Moderate/severe renal disease Moderate = creatinine >3 mg/dL (0.27 mmol/L), Severe = on dialysis, status post kidney transplant, uremia	**2**
Any tumor	Localized **2** Metastatic **6**
Leukemia	**2**
Lymphoma	**2**
AIDS	**6**

EKG: Electrocardiogram, AIDS: Acquired Immunodeficiency Syndrome

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Table II. *Age-adjusted Hematopoietic Stem Cell Transplantation Comorbidity Index*

Comorbid condition	Weight
History of arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias 1
Cardiac disease CAD = ≥1 vessel coronary stenosis requiring medical treatment, stent, or CABG	Coronary artery disease, congestive heart failure, myocardial infarction, or EF ≤50% 1 Valvular disease (except mitral prolapse) 3
Inflammatory bowel disease	Crohn disease or ulcerative colitis 1
Diabetes mellitus	Treated with insulin or oral hypoglycemics 1
Cerebrovascular accident or transient ischemic attack	1
Psychiatric disturbance Depression or anxiety requiring psychiatric consultation or treatment	2
Hepatic dysfunction	Chronic hepatitis, bilirubin >ULN to 1.5 × ULN, or AST/ALT >ULN to 2.5 × ULN 1 Cirrhosis or fibrosis or bilirubin >1.5 × ULN or AST/ALT >2.5 × ULN 3
Obesity (body mass index ≥35 kg/m^2)	1
Infection Requiring continuation of antibiotics after day 0	1
Rheumatologic disease	2
Peptic ulcer	2
Renal dysfunction Serum Cr >2 mg/dL (177 µmol/L), on dialysis, or prior renal transplant	2
Pulmonary dysfunction	Dyspnea on slight activity or DLCO and/or FEV1 66 to 80% 2 Dyspnea at rest or requires oxygen or DLCO and/or FEV1 ≤65% 3
Prior solid tumor Treated at any point in the patient's history	3
Type of transplant Allo-HCT = allogeneic hematopoietic cell transplant, ASCT = autologous stem cell transplant	Allo-HCT 2 ASCT 2
Age **For age-adjusted HCT-CI (allo-HCT only)**	<40 years **0** ≥40 years **1**

CAD: Coronary Artery Disease, CABG: Coronary Artery Bypass Surgery, EF: Ejection Fraction, ULN: Upper Limit of Normal, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, DLCO: The Carbon Monoxide Diffusing Capacity Test, FEV: Forced Expiratory Volume, HCT: Hematopoietic Cell Transplantation, HCT-CI: Hematopoietic Stem Cell Transplantation Comorbidity Index

2. PATIENTS and METHODS

This retrospective single-centre analysis was conducted to determine the relationship between comorbidities assessed using existing indices, and survival in adults (age ≥18 years) diagnosed with AML or Acute lymphoblastic leukemia (ALL). The study included 35 patients as 16 cases diagnosed with AML and 19 cases with ALL between 2016 and 2023. Non-relapse mortality (NRM) is more significantly influenced by pretransplant comorbidities than deaths resulting from disease progression or relapse. Therefore, patients who died due to relapse or treatment resistance were excluded. Pre-primary treatment comorbidities were assessed using the age-adjusted HCT-CI and age-adjusted CCI. The age-adjusted CCI is evaluated on a scale of 0 to 37, considering the patient's age and certain comorbidities, while the age-adjusted HCT-CI is assessed on a scale of 0 to 29 [13]. Patients were classified into low-intermediate risk (age-adjusted HCT-CI = 0, 1-2) and high risk (age-adjusted HCT-CI ≥3) groups according to the age-adjusted HCT-CI [9]. Age-adjusted CCI attributes two points for "leukemia"; therefore, patients are classified into two groups based on the age adjusted CCI scores as 0-2 and ≥3. In this study, comorbidity data were obtained from a central electronic database where each patient's diagnoses were officially coded and recorded. In addition, all medical notes in the hospital records of the patients were reviewed to attribute comprehensive information.

The study was approved by the Marmara University, Shool of Medicine Clinical Research Ethics Committee (date: 03.11.2023, approval number: 09.2023.1455). All participants provided informed consent, and the study was conducted in accordance with good clinical practice standards and in compliance with the Helsinki Declaration.

Statistical Analysis

Statistical analyses were conducted using "IBM SPSS Statistics for Windows, Version 25.0 software (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)." Descriptive statistics were presented as number (n) and percentage (%) for categorical variables and mean±standard deviation (SD) values

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for continuous variables. ROC curve analysis was utilized to analyze the predictive value of CCI and HCT-CI parameters for mortality. The Kaplan-Meier method was used to assess overall survival (OS) of the patients. A value of $p<0.05$ was considered statistically significant.

3. RESULTS

The baseline characteristics of the patients are summarized in Table III. The median age of the patients was 34 years (range, 20-65 years), and 65.7% of the patients were males. Patients diagnosed with ALL constituted 45.7% of the total, while those diagnosed with AML comprised 54.3%. In terms of genetic features, 51.4% of the patients were classified as standard risk, while 48.6% were considered high risk (Table III).

Table III. *Patient and disease characteristics*

Characteristics	n	%
Age		
Mean±SD	35.89±12.44	
Median (min-max)	34 (20-65)	
≤34	18	51.4
>34	17	48.6
Gender		
Female	12	34.3
Male	23	65.7
HCT-CI		
Low-intermediate risk	27	77.1
High risk	8	22.9
CCI		
0-2	25	71.4
≥3	10	28.6
GVHD story		
Absent	9	25.7
Present	26	74.3
Cytogenetic features		
Standart risk	18	51.4
High risk	17	48.6
Diagnosis		
ALL	16	45.7
AML	19	54.3
Progression		
Absent	17	48.6
Present	18	51.4
Mortality		
Alive	17	48.8
Dead	18	51.4
Cause of Death		
Covid-19	1	5.5
GVHD	2	11.1
Sepsis	15	83.4
Mean follow-up duration	19.80±4.94	

HCT-CI: Hematopoietic Stem Cell Transplantation Comorbidity Index, CCI: Charlson Comorbidity Index, GVHD: Graft-versus-host-disease, ALL: Acute lymphoblastic leukemia, AML: Acute Myeloid Leukemia

The 2-year NRM rate was determined to be 51.4% (Figure 1). The estimated statistics for the parameters of the age-adjusted CCI (p=0.217) and age-adjusted HCT-CI (p=0.102) were not found to be statistically significant in distinguishing the presence of NRM (Table IV, Figure 2). As seen in Table V, the overall median OS (months) could not be reached. There was no significant difference in the 2-year OS among the diagnosis groups (p=0.243) (Figure 3). The 2-year OS of patients with standard-risk genetic features was significantly higher compared to patients with high-risk genetic features (p=0.003) (Figure 4). Statistically significant differences were found in median OS (months) according to HCT-CI groups (p=0.009), and CCI groups (p=0.011) (Figures 5,6).

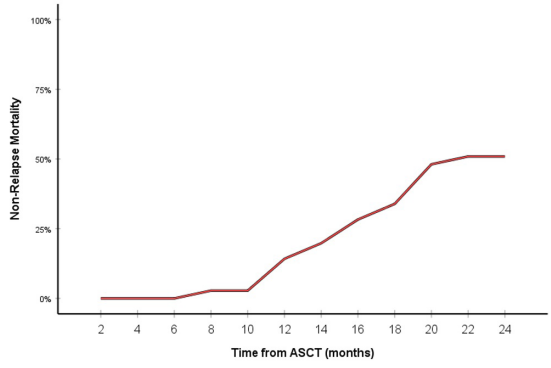

Figure 1: *The 2-year NRM rate was determined to be 51.4%.*

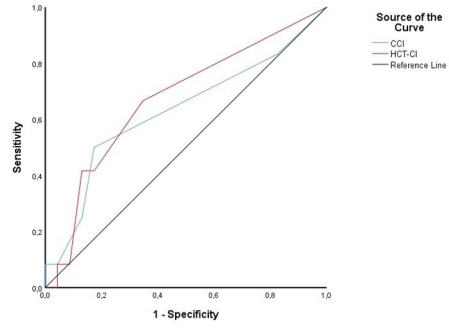

Figure 2: *ROC curves.*

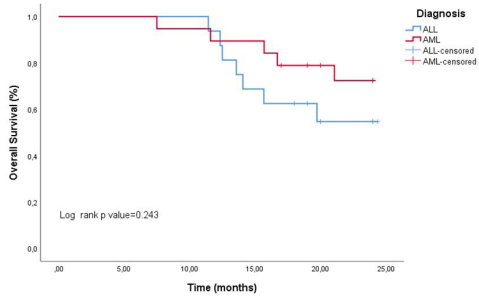

Figure 3: *There was no significant difference in the 2-year OS among the diagnosis groups (p=0.243).*

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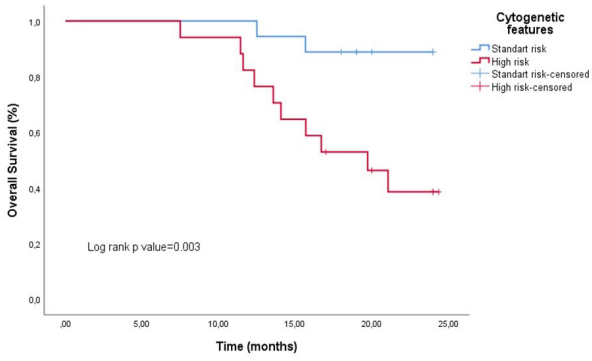

Figure 4: *The 2-year OS of patients with standard-risk genetic features was significantly higher compared to patients with high-risk genetic features (p=0.003).*

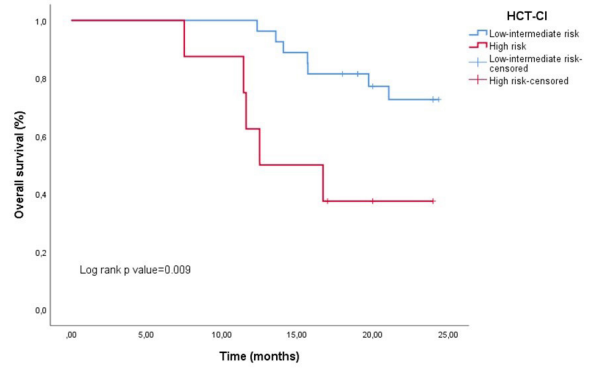

Figure 5: *Statistically significant differences were found in median OS (months) according to HCT-CI groups (p=0.009).*

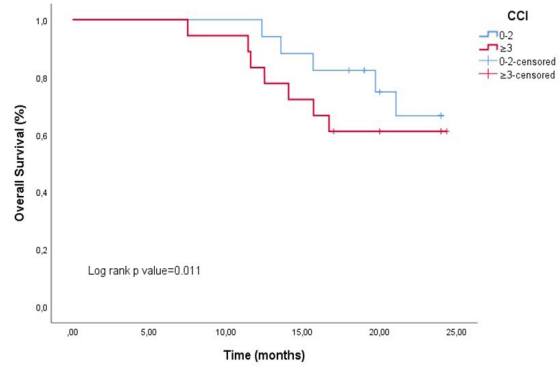

Figure 6: *Statistically significant differences were found in median OS (months) according to CCI groups (p=0.011).*

Table IV. *Analysis of the predictive values of HCT-CI and CCI values in distinguishing non-relapse mortality*

Variables	AUC	%95 CI	Cut-off	Sensitivity (%)	Specificity (%)	P
CCI	0.629	0.420-0.838	≥2.50	50.0	82.6	0.217
HCT-CI	0.670	0.477-0.864	≥0.50	66.7	65.2	0.102

AUC, Area Under the Curve; %95 CI, Confidence Interval

Table V. *Comparisons of overall survival among the patients*

Variables	2-year OS (%)	Median OS (%95 CI)	P
General	64.2	NR	
Gender			
Female	83.3	NR	0.121
Male	55.2	NR	
Age			
≤34	76.2	NR	0.067
>34	52.9	NR	
Diagnosis			
ALL	54.7	NR	0.243
AML	72.4	NR	
Cytogenetic features			
Standard	88.9	NR	**0.003**
High	38.6	19.73 (13.34-26.11)	
HCT-CI			
Düşük-orta risk	72.7	NR	**0.009**
Yüksek risk	37.5	12.50 (5.43-19.56)	
CCI			
0-2	74.4	NR	**0.011**
≥3	40.0	14.07 (7.56-20.57)	
GVHD			
Absent	66.7	NR	0.864
Present	63.6	NR	

OS: Overall Survival, HCT-CI: Hematopoietic Stem Cell Transplantation Comorbidity Index, CCI: Charlson Comorbidity Index, GVHD: Graft-versus-host-disease, ALL: Acute lymphoblastic leukemia, AML: Acute Myeloid Leukemia, %95 CI: Confidence Interval,
The Kaplan-Meier curve, Log-rank test, p<0.05 were statistically significant

4. DISCUSSION

The results of this study demonstrated statistically significant differences in median OS (months) according to risk levels (p=0.003), HCT-CI groups (p=0.009), and CCI groups (p=0.011). However, no relationship was found between age-adjusted HCT-CI or age-adjusted CCI scores and NRM. Allogeneic hematopoietic stem cell transplantation is the preferred treatment for numerous hematological conditions, both malignant and benign. Nonetheless, it carries a notable risk of NRM, primarily attributable to graft-versus-host disease and infections. The declining trend in NRM risk and the concurrent improvement in long-term survival in recent years are likely due to more adaptable conditioning regimens, enhanced donor

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selection, and improved supportive care. However, NRM continues to pose a significant challenge. Therefore, accurate prediction of OS and NRM is crucial for evaluating the risk-benefit ratio of Allo-HSCT and providing better counseling to patients.

Since, the mortality associated with Allo-HSCT is significantly high, it is necessary to assess the potential risks for patients before undergoing this procedure. Sorror et al., identified the most common medical conditions in HSCT patients to establish a scoring system for assessing the risk and survival probability after allogeneic HSCT [13]. NRM, which is often affected by pre-allogeneic HSCT comorbidities, was used instead of survival. The original report of the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) [1] is currently the most popular index for associating post-HSCT comorbidities with outcomes and included 1055 patients. This report indicated that 38% of patients scored 0 points, 34% scored 1-2 points, and 28% scored ≥3 points. The authors also concluded that the previously used CCI had a higher overall predictive value, with nearly 90% concentration in the low score [17].

The CCI has been applied across various cancer types and leukemias, such as AML, breast cancer, colorectal cancer, esophageal cancer, and non-Hodgkin's lymphomas. It has been observed that this score can also be employed for predicting OS in patients with acute leukemia [15]. Although, the HCT-CI scores demonstrated high efficacy in predicting patient outcomes post-HCT, it is essential to acknowledge that other significant pre-transplant factors also play pivotal roles. Factors such as age and disease stage of a specific hematological malignancy should be taken into consideration when assessing HCT risks [18, 19].

In our study, we observed that the age-adjusted HCT-CI and the age-adjusted CCI were effective in predicting overall survival, but it was seen that they did not effectively predict NRM. There could be several reasons for this discrepancy. One possibility is that these indices may have primarily focused on factors related to the primary disease and its impact on overall survival, but they may not have fully captured specific risk factors associated with nonrelapse mortality, such as graft-versus-host disease and infections. In addition, the development and progression of NRM may be influenced by a variety of factors beyond those assessed by these indices, including patient-specific factors, transplant-related complications, and variations in treatment protocols. Further research may be needed to identify additional predictive factors specifically related to NRM in the context of hematopoietic stem cell transplantation, or to refine these indices.

The ALFA-9803 trial evaluated the impact of pre-treatment comorbidities on survival in a large cohort of 416 AML patients aged ≥65 years treated with intensive therapy. The multivariate analysis model results showed that age ≥75 years, performance status (PS) ≥2, infection, HCT-CI, white blood cell (WBC) >50×109/L, and high-risk cytogenetics were independent adverse risk factors for survival. The HCT-CI score, high-risk cytogenetics, and infection at baseline predicted 4 and 12-month OS as initially predefined. However, neither HCT-CI nor infections reached the 10% predefined prevalence level. It should be noted that only 5% of patients in this cohort had HCT-CI ≥3 due to the exclusion criteria. Age, PS, and WBC count needed to be associated to achieve a high specificity. High-risk cytogenetics was the only independent strong risk factor. A risk score was developed, including high-risk cytogenetics and/or at least two of the following parameters (age ≥75 years, PS ≥2, and WBC >50×109/L). Patients received intensive therapy if they had no risk factors, and the others were offered alternative therapies. This two-class decisional index identified 24% of patients with a lower 1-year survival rate of 19% [20].

Although, several studies have shown that waiting for cytogenetics does not have an impact on induction treatment outcome, many hematologists feel compelled to start treatment before cytogenetics data are available [21, 22]. Scarce material quality or an incomplete metaphase quantity may also be reasons for the unavailability of cytogenetic information at the initiation of treatment. The CCI and HCT-CI can be determined without cytogenetic or molecular data.

Allogeneic hematopoietic cell transplantation (allo-HCT) holds potential as a curative treatment for specific patients with hematological diseases. Various factors influence the outcomes, and clinical judgment often guides patient selection [23]. However, allo-HCT comes with a notable risk of NRM, especially in the presence of comorbidities and among older patients [24]. NRM is commonly associated with graft-versus-host disease, organ toxicity, and infectious complications. Patient age, comorbidities, donor type, remission status, and the conditioning regimen used are among the parameters that can significantly impact outcomes [9, 25, 26]. Therefore, it is essential that a thorough pre-transplant assessment must be conducted to assess the risks and benefits associated with allo-HCT.

Limitations

There were several limitations to this study. First, the retrospective nature of the data collection, as reliance on data recorded in medical charts might have resulted in the omission of potentially important information, which could then have been excluded from this analysis. However, the introduction of laboratory and functional data, most of which were stored in the database, reduced the likelihood of missing comorbidities. New protocols should include prospective scoring of enrolled patients to be able to better address this issue.

Another limitation of the study was the heterogeneity of both preparative regimens and disease types. The retrospective nature of the analysis was a potential source of bias, although, age-adjusted HCT-CI scores and age-adjusted CCI scores were collected prospectively. Nevertheless, the importance of assessing single-centre data to be able to realistically predict post-transplant outcomes within that centre has been emphasised in this study. New research approaches may need to be developed for pre-transplant risk calculation that can be applicable to patients from various centres characterized by heterogeneous practices.

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Conclusion

It is encouraging to include formal comorbidity scoring, using age-adjusted HCT-CI and age-adjusted CCI in the initial assessment of patients with acute leukemia and those under 65 years old. It seems reasonable to classify patients for current treatment or protocol entry based on their age-adjusted HCT-CI and age-adjusted CCI scores. However, it was noted that these indices were not effective in predicting NRM. When predicting NRM, it is important to acknowledge the critical roles played by other significant pre-transplant factors. Factors such as the genetic risk of the disease, conditioning regimens, and donor type should be carefully considered.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University, Shool of Medicine Clinical Research Ethics Committee (date: 03.11.2023, approval number: 09.2023.1455). All participants provided informed consent, and the study was conducted in accordance with good clinical practice standards and in compliance with the Helsinki Declaration.

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Exam-related changes in salivary oxytocin and cortisol levels of preclinical medical students

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ABSTRACT

Objective: The relationship between exam conditions with the peripheral oxytocin and cortisol levels and psychological characteristics by gender were investigated.

Participants and Methods: Thirty-six preclinical medical students gave saliva samples in exam-free and pre-and post-exam conditions and completed a comprehensive psychometric questionnaire.

Results: Before the theoretical exam, cortisol levels were elevated in females but not in males, whereas, oxytocin levels were similar in both sexes under exam conditions. Genders were equalized in terms of most psychometric properties. Females did not feel prepared for the exam and experienced more anxiety before the exam than males. Females had higher cortisol levels before the exam than after the exam, but no change was observed in the cortisol levels of males by the exam conditions. Oxytocin levels did not differ significantly for any condition or group.

Conclusion: Females may need to be supported in study planning and time management to increase exam preparedness and stress management to increase coping with stress. The study's small sample size casts a shadow on the generalizability of the results. In future studies, the research process can be spread over a longer period and more people can be reached by not giving up strict selection rules.

Keywords: Test anxiety, Medical education, Oxytocin, Gender, Cort

1. INTRODUCTION

A safe academic environment supports academic development and positively affects the moral constructs and behaviors of medical students [1, 2]. However, the undergraduate medical education is regarded globally as a long, stressful and anxiety-provoking stage [3-5]. It was emphasized that taking an exam or having poor academic performance was associated with high levels of perceived stress and cortisol in the university students [6-8]. In parallel, mental health of medical students was negatively affected during their training, and higher levels of perceived stress, anxiety and depressive symptoms were evident as compared to non-medical students [9-12]. A recent study demonstrated that physical and mental health of students were worsened at the end of the first-year of the medical training, but were then improved throughout the rest of the education, while perceived stress levels have still remained high [13].

The neuropeptide oxytocin (OXT) was proposed to exert anti-stress and anti-anxiety effects [14, 15]. Studies have shown that activation of the hypothalamo-pituitary-adrenal axis (HPA), induced by a psychosocial stress causes a cortisol response, which is accompanied by an elevated OXT secretion showing a positive correlation with the elevated cortisol levels [16, 17]. It was suggested that the stress-relieving effect of OXT does not occur at the initial phase of the HPA hyperactivity, but high levels of OXT secretion accelerates vagal recovery during the later phase of stress [17]. On the other hand, stress reduction activities and social engagement are proposed to yield an enhanced secretion of OXT and a resultant vagal upregulation [18, 19].

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One of the major causes of stress among university students is the "exam anxiety", which may frequently disturb academic performance and result in several psychological problems [20, 21]. The impact of exam anxiety was evaluated in non-medical students, and salivary cortisol concentrations were found to be elevated before the exams with a higher cortisol response in the oral exams as compared to written tests [7, 22-24]. The facilitating effect of oxytocin on coping with stress has been examined in terms of situations that cause social stress: Studies show that intranasal OXT intake reduces social stress-induced anxiety in women, increases the positive effect of social support [25], and decreases cortisol concentration in stress situations with interpersonal difficulties [26]. Endogenous OXT rises before cortisol when the exam period approaches and contributes to the management of the stress response by regulating the effect of cortisol, which subsequently increases [27]. However, the contribution of OXT response to exam-induced anxiety in medical students, and the impact of gender, coping styles, social relationships and the personality characteristics on their exam-induced anxiety were not elucidated before. Since exam stress and how this stress is managed may be related to a number of psychometric properties, personality and cognitive characteristics of the participants and their coping styles were also evaluated in the present study with valid and reliable scales. While evaluating the relationship between gender, exam condition, cortisol and OXT levels, if a difference has arisen in any of the mentioned psychometric features, the correlation between this feature and stress-induced CORT and OXT response was also examined.

The aim of the present study was to investigate the effect of anticipated written exams on the salivary OXT and cortisol responses of the pre-clinical medical students who were evaluated in various psychometric characteristics. The main hypotheses of the study were as follows: 1. Females have a higher pre-exam anxiety level than males; 2. Females have higher CORT levels before and after the exam; 3. OXT levels in females both before and after the exam are higher than those in males.

2. PARTICIPANTS and METHODS

Participants and the research design

The study was approved by the Marmara University, School of Medicine, Ethics Committee for Clinical Research (06.03.2016-09.2016.390). The aim and the inclusion criteria of the study were announced on the Marmara University School of Medicine (MUSM) campus using the bulletin boards, and three meetings were held by the researchers to explain the procedures. Inclusion criteria were determined as: not having diagnosed with a psychological or a neurological disease, not having a systemic disease, not being pregnant or lactating, not smoking and not being on a legal or an illegal drug during the study period.

Forty-one students studying at MUSM participated in the study. Despite regular calls for participation in the research, the number of participants could not be increased more. On the other hand, 5 students missed one or two salivary measurements, and thereby the statistical analyses were executed by using the data of 36 students (19 females and 17 males with a mean age of 18.97± 0.86 years), which revealed a similar sample size that has been used in many studies, as reported in the meta-analysis of Spilijak et al. [28]. The participants were at the 1st (n=11), 2nd (n=7), or 3rd (n=18) year of the medical school at the time of the research. During these preclinical years, the theoretical exams for different subject committees are prepared in similar formats and are given as multiple-choice exams to be answered within 90 to 100 minutes. In order to eliminate a possible bias in the study that could be caused by the participation of high-achieving students, exam performance data were compared with the median of the whole class using a one-sample non-parametric test and the results indicated that the median of the study sample is not significantly different from that of the whole class (data not shown).

In an exam-free period (45 to 60 days before the exam) students were gathered in groups in one classroom, where all the questionnaire-filling and saliva-collecting activities would be done, and then they were given a training on the saliva collection method (Figure 1). During this session, they were also asked to fill in two questionnaires. Within the same week, they were asked to come over again to fill in a second set of questionnaires, and to collect their baseline saliva samples. During this second session, the students stated on the given forms whether they have experienced any stressful events within the last 6 months and the severity degree of the experienced stress. A day before the collection day (baseline or exam day), the students were sent an e-mail or a text message which reminded them the time and requirements for saliva collection. The times at which saliva samples were collected during the exam-free period were matched with the times at which saliva samples were collected during the exam period (between 09:00 am to 10:00 am and 11:30 am to 12:30 pm).

Before exams, the students were asked to what extent they felt ready for the exam (1-I am not ready to 5-I am too ready) and how anxious they were about the exam (1-I am not worried at all 5-I am extremely worried). At 30 min before the exam, and at 15 min immediately after the exam, the students collected their saliva into tubes.

Questionnaires and Inventories

People's responses to stress situations can be determined by many factors including environmental, physiological and psychosocial. In this study, all students were undergoing the same examination system and strict selection criteria were used to eliminate possibilities that could affect the physiology of the individual. In addition to these, certain personality traits can be related to appraisal, coping styles and coping effectiveness [29]. Burgess et al., showed a positive correlation between "agreeableness" and problem-focused coping strategies [30]. Also, a significant negative correlation exists between "agreeableness" and negative emotional reactions [31]. Since, the metacognitions are closely related to different dimensions of test anxiety [32, 33], the need for controlling thoughts, cognitive confidence, and negative beliefs about the uncontrollability of

thoughts and danger were reported to be positively correlated with anxiety [34, 35]. Also, People may activate different coping mechanisms in line with their personality traits and different circumstances [36]. Problem-focused coping predicted the reduction of academic stress [37] and decreased cortisol levels [38]. Due to these variabilities in effect, this study included comprehensive psychological tools to measure possible individual differences.

The research sample was evaluated in terms of the following psychometric features that may be related to coping with stress. The Scale of Dimensions of Interpersonal Relationships, which has 53 items with 4 dimensions, was used to predict the interpersonal relationships [39]. The Cronbach's alpha coefficients of this scale's dimensions vary between 0.78 and 0.85. The Turkish version Metacognition Questionnaire-30 (MQ-30) was adapted by Tosun and Irak and, has 30 items with 5 dimensions [40]. Any increase in the scores means that the specific metacognitive activity has increased and may cause anxiety in the participants. The Ten-Item Personality Inventory was also adapted to Turkish and it consists of 10 items and 5 dimensions [41]. The Cronbach's alpha values of the dimensions vary between 0.81 and 0.86. The higher the score for a dimension, more dominant is the dimension as a personality trait for the participant. MQ-30's total Cronbach's alpha score is 0.93 and its dimensions' Cronbach's alpha values are between 0.72-0.93. Brief Coping Styles Scale's (COPE) validity and reliability study was done by Bacanlı et al., and, the dimensions' Cronbach's alpha values vary between .39 and .92. It has 28 items and shows a 14-factor structure [42]. State-Trait Anxiety Inventory (STAI) was used only to measure "state anxiety" using a 20-item form with one dimension [43]. The Cronbach's alpha coefficient for the state anxiety inventory is 94. Higher scores in STAI indicate greater anxiety.

Collection of saliva samples and the measurement of salivary oxytocin and cortisol levels

Saliva collection was first made during the exam-free period and then repeated before and after the exam (Figure 1). By collecting saliva samples, it was aimed to eliminate the anxiety of repeated invasive sampling by blood withdrawal [44]. The students were asked to wash their mouth with water and spit it out. They were then instructed to place a roll of cotton (SalivaBio Oral Swab, Salimetrics, Carlsbad, CA, USA) under their tongue, tilt their head forward and accumulate saliva in their mouth without swallowing for 40 s. Then, the students with their surgical gloves on, placed the wet cottons into the Salivettes® (Sarstedt, Rommersdolf, Germany) that were previously labeled with codes. The Salivettes were kept ice-chilled for at most 1 h until they were centrifuged at 4 °C and 1500 g for 15 min. The liquid samples obtained after centrifugation were then stored at −80 °C. Salivary OXT and cortisol levels were measured using the commercial enzyme linked immunosorbent assay (ELISA) kits (Human OXT Cat. Number: 201-12-1047; Human cortisol Cat. Number: 201-12-1004; Sunlong Biotech, China). OXT level was expressed in ng/μg protein with a sensitivity of 1.775 pg/ml and cortisol levels in nmol/μg protein with a sensitivity of 7.186 nmol/L. After each saliva collection, sandwiches and fruit juices were offered to all students.

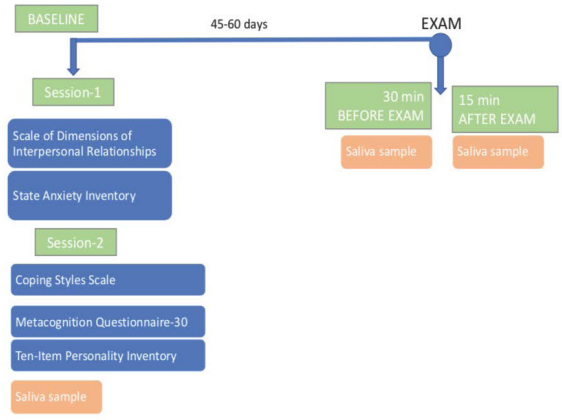

Figure 1. *Psychometric measurement and biological data collection design*

Statistical Analysis

The sample size was determined with the OpenEpi program (https://www.openepi.com/). Estimating the difference in saliva cortisol level between the groups [45], sample size was calculated as n=16 with 80% power and 95% Confidence interval (2-sided).

Saliva levels of OXT and cortisol were analyzed by One-Way repeated measures of ANOVA using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA) program. Jamovi 2.3.21 was used to compare genders in psychometric properties. The Mann-Whitney U were used due to the low sample size and not normal distribution. Significance level was determined as $p<0.05$ and Bonferroni correction was used when necessary.

3. RESULTS

Psycho-biological characteristics of the participants

Table I shows the mean and median scores for each psychometric measurement, gender differences and baseline biological variables. Mean salivary OXT and cortisol changes for genders are presented in Figure 2 and 3. In females, cortisol levels measured before the exam were higher than the cortisol levels determined after the exam ($p=.047$). However, salivary cortisol levels in males were not significantly different among measurements ($p>.05$). OXT levels in males or female students have not significantly changed before or after the examination (for both males and females $p>.05$).

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Table I. *The inventory/questionnaire scores and baseline salivary cortisol/oxytocin levels in the baseline conditions.*

Metacognition Questionnaire-30				
	Min-max score can be obtained	Mean (Standard deviation)	Median	Interquartile ranges
Positive beliefs about worry	7-24	14.83 (3.74)	15.50	5.75
Negative beliefs about uncontrollability of thoughts and danger	7-28	15.20 (3.40)	15.00	6
Cognitive confidence	6-24	12.29 (4.45)	12.00	5.25
Cognitive self-consciousness	1-24	18.42 (3.16)	18.00	4
Beliefs about need to control thoughts[a]	1-20			
All participants		13.97 (3.28)	14.00	6
Female		15.10 (3.26)	16.00	5
Male		12.62 (2.84)	11.00	4
Ten-Item Personality Inventory				
Emotional stability	2-14	8.41 (2.07)	8.00	3
Openness to experiences	2-14	7.94 (1.63)	8.00	2
Conscientiousness	2-14	7.97 (2.20)	8.00	3.25
Extraversion	2-14	8.97 (1.69)	8.50	2
Agreeableness	2-14	8.66 (2.24)	8.00	2.5
Brief Coping Styles Scale				
Using Instrumental Social Support	2-8	6.48 (1.29)	7.00	1
Humor	2-8	5.41 (1.84)	5.50	3
Substance use	2-8	2.22 (0.76)	2.00	0
Acceptance	2-8	6.63 (1.37)	7.00	2
Denial	2-8	4.77 (0.98)	5.00	2
Behavioral Disengagement	2-8	2.82 (1.01)	3.00	1
Mental Disengagement	2-8	5.16 (1.34)	5.00	2
Suppression of Competing Activities	2-8	5.80 (1.25)	6.00	2
Turning to Religion	2-8	6.08 (1.90)	6.50	3.75
Restraint coping	2-8	4.97 (1.38)	5.00	2
Positive Reinterpretation	2-8	6.36 (1.33)	6.00	2
Planning	2-8	7.08 (1.15)	7.00	1.75
Focus on and Venting of Emotions	2-8	5.41 (1.22)	5.00	1.75
Using Emotional Social Support[b]	2-8			
	All participants	5.66 (1.24)	6.00	2
	Female	6.10 (1.04)	6.00	1
	Male	5.17 (1.28)	5.00	2
Scale of Dimensions of Interpersonal Relationships				
Approval dependence	15-60	35.88 (8.09)	36.00	11
Empathy	9-36	29.45 (3.43)	29.00	5
Trust for others	15-60	42.46 (4.41)	41.50	6
Emotional awareness	14-56	42.91 (4.80)	43.50	7.25
State Anxiety Inventory (min 20 – max 80 for the inventory)				
	20-80	35.63 (7.54)	35	10.75
Cortisol in saliva (nmol/µg protein) in the non-exam period				
		4.76 (1.78)	4.85	2.86
Oxytocin in saliva (ng/µg protein) in the non-exam period				
		4.97 (2.47)	5.15	2.79

Note. All data were compared regarding the gender of the students. Except the indicated statistical significances, the rest of the data were not different between males and females.
a Females have higher scores than males (U=83.5, z=-2.28, p= .002)
b Females have higher scores than males (U=86.00, z=-2.46, p= .013)

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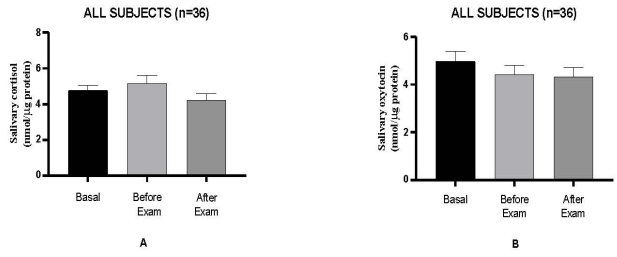

Figure 2. *Salivary cortisol (A) and oxytocin (B) levels in all students*

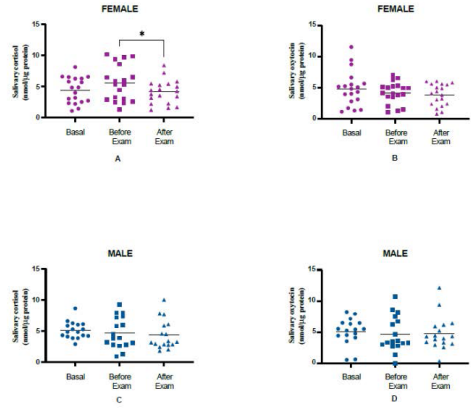

Figure 3. *Salivary cortisol (A & C) and oxytocin (B & D) levels in females (n=19) and males (n=17) * p<0.05*

Perceived stress, perceived preparedness before the exam

Subjective anxiety before the written exam was higher in females than that in males (U = 66.50, z = – 1.85, p = .033) (For females 3.56 (SD=1.09), *Median* = 3, for males *2.75 (SD=.096) Median =3)*. For the written exam, the males' level of feeling prepared for the exam was 3.58 out of 5 (*SD* = .96, *median*=3.5), that of the females was 2.47 (*SD*= .72, *median*=3.0) (U = 43.00, z = – 3.05, p = .001). There was a negative correlation between feeling prepared before the theoretical exam and cortisol levels before the exam (r=-.627, p=.01) and after the exam (r=-.511, p=.01) only in women.

Psychological variables in relation to biological differences

Most of the psychometric characteristics of the participants were similar between genders which helped us to attribute the differences in biological changes to the exam type and related perceived stress. Only in "Beliefs about need to control of thought" and "Using emotional social support" dimensions females had higher scores than males (Table I). The aforementioned correlation for females between perceived readiness for the exam and cortisol levels before and after the exam was checked by partial correlation analysis by controlling for those dimensions. The correlation between perceived preparedness and before exam cortisol levels was still significant (p=.028). Also, the correlation between perceived readiness and cortisol levels after the exam was verified for females even after controlling for the psychometric dimension (p=.016).

4. DISCUSSION

Our data revealed that salivary cortisol levels of the female students were significantly elevated before the exam, but the salivary cortisol levels of the male students were not altered by the exam, while no statistically significant difference was present among the salivary OXT levels of male or female students. Brown et al. [46] pointed out that there was no correlation between the gender distribution and the peripheral OXT and cortisol concentrations, but others [47] have indicated sex-related differences in the cortisol levels. The elevated cortisol response in the female students may be explained by their lower perceived readiness as compared to males, which was reported by the students before the exam. Other studies have also shown that female students experience more stress than male students [48-51] and especially the academic stress in male students is reduced during the school years, while the stress level of female students remains the same throughout the education [48, 52]. Taken together, higher readiness and lower test anxiety of the male students may explain their unchanged cortisol levels before the theoretical exam.

In contrast to their higher salivary cortisol levels, the OXT levels of female students were not changed before the written exam. The emergence of a stressful situation or receiving social support when a stressful stimulus is experienced cannot always be associated with the OXT response and different experimental designs can have confounding effects [13, 53, 54]. People may activate different coping mechanisms in line with their personality traits under different circumstances [36].

Some studies have reported a correlation between metacognitions and test anxiety [32, 33]. However, the MCQ-30 dimension that predicts test anxiety is generally the "negative beliefs about the uncontrollability and danger of worry" dimension [34, 35]. Therefore, it can be expected that the dimension "beliefs about need to control thought", which is a different dimension than the one mentioned above, does not change the correlation between feeling prepared before the exam and cortisol.

The main limitation of this study is that a larger sample size could not be reached. Possible reasons for this may be the strict criteria for inclusion in the study and the choice of not participating in a practice that may create extra stress before the exams, which is already a stressful situation. In future studies, it may be beneficial to reward participation in order to increase the motivation of students to participate. Since the sampling was made at 15 min before and after the exam, the hormonal responses were detected at these time points. Future studies could be planned to make saliva sampling at more frequent intervals in the exam room immediately before and after the stressor, which was not applicable to exam rules in our institution. On the other hand, the study is based on the comparison of gender groups that are largely similar in terms of some personality traits and coping styles, showing no difference between the baseline biological measurements, it provides reliable results about

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the change in biological data due to exam anxiety. In further studies, exam conditions requiring active communication with another individual can be selected or experimentally created to capture the possible change in OXT. In addition, semi-structured interviews with students can be conducted before and after the exam to reveal their metacognitions, coping styles, and perceptions of interpersonal relationships. Thus, it may be more accurate to interpret biological measurements based on cognitions at the time of the measurements.

Although, the differences observed in cortisol levels in the study differed according to gender, the findings suggest certain recommendations that are appropriate for all medical students. In the training program, it may be considered to implement practices that support students, especially female students, in stress management. These practices could include guidance and psychological counseling to provide a realistic basis for self-assessment of anticipatory performance and competence, regulation of unrealistically high expectations, effective studying and development of self-regulated learning skills during the course period prior to stressful situations such as examinations, which could help manage academic anxiety.

As both the related literature and this study show, academic anxiety can be high among students in the faculty of medicine. Considering that one of the environmental variables that determine coping with anxiety is the structure of the education program, the following can be suggested for this study: Institutionally, designing the assessment and evaluation system in a way that supports learning, reasonably organizing the time, place and duration of exams, ensuring exam validity and reliability, and using exams not only for decision-making but also for formative purposes will reduce students' uncertainty about exams and make it easier for them to see exams as a natural and learning-supportive part of education, which can have a positive impact on coping with academic anxiety.

Conclusion and limitations

Our data suggest that in preclinical medical school students, the cortisol levels of the females measured before the exam were higher than those of the males, implicating a higher stress level in females. However, oxytocin levels were similar in the exam conditions of both genders.

Strict selection rules were applied to minimize the possibility of biological data being influenced by variables other than test stress. However, this also limited the number of participants. In addition to the aforementioned selection rules, it was also questioned whether the participants had recently experienced stress for another reason. Nevertheless, the study population may have differed from the study universe at certain points. For example, curiosity about scientific research, being in contact with researcher professors. Those who did not participate in the study despite meeting the criteria may not have wanted to increase their existing anxiety because the study covered the exam period, or they may not have wanted to disrupt the order they were used to for reasons such as extra anxiety or biological sampling. Therefore, these characteristics and their effects may not have been reflected in the results.

The fact that there was no difference in cortisol for males but there was for females may be related to the fact that girls experience academic stress more intensely, as mentioned in the introduction. In this study, females felt less prepared for the exam during the exam period and this may be related to the fact that they were more anxious. The fact that oxytocin levels did not differ according to exam periods and gender can be explained by the view that changes in biological measurements may not always reflect those in psychometric measurements [13, 32, 33].

In this study, saliva was analyzed in order not to put the participants under extra stress and to prevent the inclusion of participants who might be concerned about invasive methods and to reduce the sample size further. Blood analyses would have provided more robust results and a clearer correlation with psychometric measurements, but the non-invasive method was not preferred for the reasons mentioned above.

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Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University School of Medicine Ethics Committee for Clinical Research (06.03.2016-09.2016.390).

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Author contributions: SYI, FEB, SS and BCY: Research design, SYI, FEB, SS, SAT and BCY: Methods, SYI, SS, BCY and SAT: Data collection, SYI, SS and BCY: Statistical analysis, SYI, FEB, SS, SAT and BCY: Manuscript preparation. All authors read and approved the final manuscript.

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Carotid intima-media thickness correlated with age and pulse wave velocity in ANCA-associated vasculitis patients

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ABSTRACT

Objective: Cardiovascular diseases are the main causes of mortality in the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) patients. Carotid intima-media thickness (CIMT) measurement and pulse wave velocity (PWV) were performed to determine atherosclerosis and arterial stiffness as cardiovascular risk markers.

Patients and Methods: The data of 31 patients with AAV were compared with 21 healthy controls. Demographic and laboratory findings were recorded.

Results: Seventeen patients (54.8%) were male. Mean age was 52.6±11.5 years. CIMT was higher in the patient group [0.74 (0.65 – 0.84) vs 0.63 (0.57-0.74) mm; p=0.048]. PWV [7.9 (6.7-9.3) vs 7.8 (6.8-8.5) m/s; p=0.295] and augmentation index (AI) [22.5 (11.0-30.0) vs. 23 (9.5-30.5) mm/Hg, p=0.801] were similar in both groups. CIMT was correlated with age (r: 0.538, p<0.001) and PWV (r: 0.554 p< 0.001) while there was no correlation with AI (r: 0.047, p= 0.764).

Conclusion: The present study showed that CIMT is significantly increased and correlated with age and PWV in patients with AAV compared to controls. CIMT can be used as a screening tool as part of patient follow-up to identify patients at cardiac risk.

Keywords: ANCA-associated vasculitis, Cardiovascular risk, Carotid intima media thickness, Pulse wave velocity

1. INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of diseases characterized by inflammation of small vessels which may affect the cardiovascular system. The cardiovascular (CV) system is rarely involved in AAV, however it is associated with poor prognosis when present. A significant number of patients undergo major CV events and CV disease is still the leading cause of death after the first year [1,2]. Therefore, we need to monitor and diagnose patients at risk for CV disease at an early stage.

Arterial stiffness is associated with CV disease and may indicate the early phase of atherosclerosis regardless of symptoms [3]. We used pulse wave velocity (PWV) and augmentation index (AI) to assess arterial stiffness. Pulse wave analysis is a non invasive and an easy diagnostic tool for assessing arterial stiffness [4]. Likewise, increased carotid artery intima-media thickness (CIMT), correlates with severity of coronary atherosclerosis and cardiovascular risk [5]. Therefore, arterial stiffness and CIMT may predict atherosclerosis before clinically overt CV disease develops and may help clinicians reduce CV disease related morbidity and mortality.

In the current study, we investigated CIMT and PWV for detecting subclinical cardiovascular disease in patients with AAV.

2. PATIENTS and METHODS

Study population

The study conforms with the Declaration of Helsinki and was approved by the Marmara University, School of Medicine, Ethics Committee (date/no: 2018/09.2018.653). Written informed consent was obtained from all participants.

Patients were followed up at the nephrology outpatient clinic where the study was conducted. Thirty-one AAV patients

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and 21 sex and age-matched controls were enrolled. Patients were excluded if they were known to have valvular heart disease, coronary artery disease, cardiomyopathy, heart failure, arrhythmia, peripheral arterial disease, poor echogenicity, end-stage chronic renal disease or malignancy. Demographic data and medical history including disease duration, disease activity, damage scores, current and past cumulative doses immunosuppressive treatments were recorded. Complete blood count and biochemistry tests were done following a 12-hour fasting period.

Assessment of CIMT

Carotid intima media thickness was measured by Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway echocardiography/ultrasonography system provided with a 10 MHz linear transducer. The same operator blindly performed all of the measurements. CIMT was measured from the first echogenic line to second echogenic line bilaterally at the common carotid artery bifurcation. The longitudinal view of the far wall of the distal common carotid arteries was used during the diastolic phase. CIMT was calculated as mean of three measurements on each side. If a plaque existed, no measurement was carried out on these sites.

Assessment of arterial stiffness parameters

Arterial stiffness was assessed after a fasting of 12 hours in all subjects in the supine position in a temperature controlled room (22-24°C). PWV and AI were measured according to current guidelines by a Mobil-O-Graph arteriography system (Mobil-O-Graph NG, Stolberg, Germany) which detects signals from the brachial artery. PWV and AI were adjusted for a heart rate of 75 bpm.

Statistical Analysis

SPSS (version 22.0; SPSS Inc, Chicago, IL) statistics package was used for statistical analysis. Categorical variables were presented as numbers and percentages and compared with the Chi-square test. Continuous variables were presented as mean ± standard deviation. Continuous variables with parametric distribution were compared with independent samples t-test and those without normal distribution were compared with Mann-Whitney U-test. Kolmogorov-Smirnov or Shapiro Wilk tests were performed to determine whether continuous variables were normally distributed. According to the normality tests, those with $p \geq 0.05$ were considered to be normally distributed. Spearman's correlation analysis performed for correlation analysis between CIMT, PWV and AI. For all statistical analyses, a p-value <0.05 was considered significant.

3. RESULTS

The study population included 31 patients with AAV and 21 controls. Twenty patients (64.5%) had a diagnosis of granulomatosis with polyangiitis (GPA) and 11 patients (35.5%) had a diagnosis of microscopic polyangiitis (MPA). Thirteen patients (41.9%) were positive for perinuclear (p)-ANCA and 18 (58.1%) were positive for cytoplasmic (c)-ANCA at diagnosis. The echocardiographic findings of the patient cohort have been reported previously [6]. The demographic and laboratory data are shown in Table I. There was no difference in sex and age among the study groups. Mean patient age was 52.6±11.5 years and 17 (54.8%) of the patients were male. Duration of disease was 36 months (18-91 months). Frequency of hypertension (HT) [14 (45.2%) vs. 1 (4.8%), p= 0.001] and mean systolic blood pressure [133.4 ± 17.9 vs. 120.9 ± 12.7, p= 0.008] were significantly higher in patients with AAV compared with controls. Serum triglyceride (204.06 ± 11.92 vs. 128.30 ± 102.67 mg/dl, p=0.019), creatinine (1.36 ± 0.71 vs. 0.71±0.17 mg/dl, p< 0.001) and C-reactive protein (CRP) (7.16 ± 9.03 vs. 3.50 ± 0.70 mg/L, p= 0.032) levels were significantly higher in patients compared with controls.

Table I. *The clinical and biochemical characteristics of the study populations.*

	Patients n:31	Controls n:21	P
Age, years	52.6 ± 11.5	51.9 ± 12.1	ns
Male gender, n (%)	17 (54.8%)	11 (52.4%)	ns
BMI, kg/m^2	28.4 ± 17.3	27.4 ± 3.4	ns
Hypertension, n (%)	14 (45.2%)	1 (4.8%)	0.001
Systolic blood pressure, mmHg	133.4 ± 17.9	120.9 ± 12.7	0.008
Diastolic blood pressure, mmHg	85.9 ± 15.1	79.4 ± 9.9	ns
Diabetes mellitus, n (%)	4 (12.9%)	1 (4.8 %)	ns
Birmingham vasculitis activity score	2.77 ± 1.94		
Vasculitis damage index	2.23 ±1.50		
Current steroid use, n (%)	15 (48.4%)		
Current azathioprine use, (%)	14 (45.2%)		
Current methotrexate use, (%)	2 (6.5%)		
Current rituximab use, (%)	15 (48.4%)		
Cumulative steroid dose, mg	10518 ± 7545		
Cumulative cyclophosphamide dose, mg	11852 ± 48445		
Cumulative azathioprine dose, mg	112994 ± 145068		
Cumulative rituximab dose, mg	3936 ± 4328		
Glucose, mg/dl	91.6 ± 15.4	92.5 ± 10.2	ns
Creatinine, mg/dl	1.36 ± 0.71	0.71 ± 0.17	<0.001
Total cholesterol, mg/dl	233.52±55.25	202.15±47.30	ns
LDL cholesterol, mg/dl	139.74 ± 42.05	122.74 ± 39.96	ns
HDL cholesterol, mg/dl	53.52 ± 14.71	55.05 ± 16.31	ns
Triglyceride, mg/dl	204.06 ± 11.92	128.30 ± 102.67	0.019
CRP (mg/L)	7.16 ± 9.03	3.50 ± 0.70	0.032

ANCA: Anti-neutrophil cytoplasmic antibody; **BMI**: Body mass index; **c-ANCA**: Cytoplasmic: Anti-neutrophil cytoplasmic antibody; **CRP**: C reactive protein; **HDL**: High density lipoprotein; **LDL**: Low density lipoprotein; **p-ANCA**: Perinuclear anti-neutrophil cytoplasmic antibody. ns: non significant

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Carotid artery intima-media thickness was significantly higher in AAV patients [0.74 (0.65-0.84) vs. 0.63 (0.57-0.74), p=0.048], however, PWV pulse wave velocity [7.9 (6.7-9.3) vs. 7.8 (6.8-8.5) m/s, p=0.295] and AI [22.5 (11.0-30.0) vs. 23 (9.5-30.5) mm/Hg, p=0.801] were similar in both groups (Table II). CIMT was correlated with age (r: 0.538, p< 0.001) and PWV (r: 0.554 p< 0.001) while there was no correlation with AI (r: 0.047, p= 0.764) (Figure 1 and 2).

Table II. *Comparison of carotid intima-media thickness, pulse wave velocity and augmentation index between AAV patients and controls.*

	Patients n: 31	Controls n: 21	P
Carotid intima-media thickness, cm	0.74 (0.65-0.84)	0.63 (0.57-0.74)	0.048
Pulse wave velocity, m/s	7.9 (6.7-9.3)	7.8 (6.8-8.5)	ns
Augmentation index, mmHg	22.5 (11.0-30.0)	23.0 (9.5-30.5)	ns
ns: Non significant			

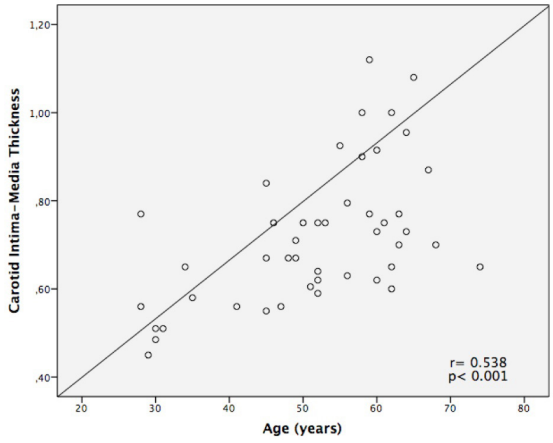

Figure 1. *Correlation analysis between carotid intima-media thickness and age*

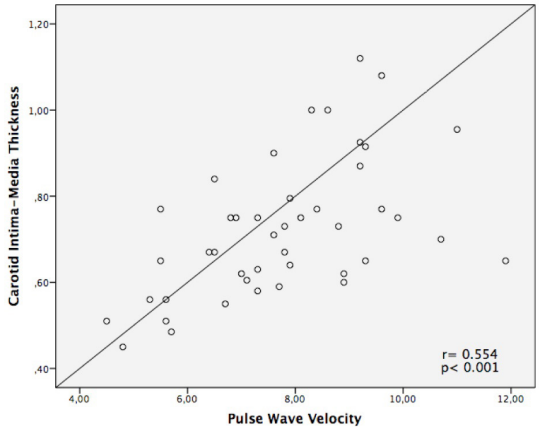

Figure 2. *Correlation analysis between carotid intima-media thickness and pulse wave velocity*

4. DISCUSSION

The main finding of the present study is that CIMT is significantly increased and correlated with age and PWV in patients with AAV compared to controls. Arterial stiffness, as assessed by PWV and AI, was similar in both groups. Despite the fact that cardiovascular disease is one of the most common causes of mortality in AAV patients, overt cardiac disease is rare [7,8]. On the other hand, AAV is characterized by vascular inflammation which can cause endothelial dysfunction, leading to subclinical atherosclerosis [9,10].

In our study, we found that CIMT was higher in AAV patients compared to control subjects. CIMT is considered an early atherosclerosis marker which is associated with cardiovascular risk [4,11]. Thus, increased CIMT may explain the increased incidence of CV disease in this patient group. Hatri et al., measured CIMT in 64 Takayasu arteritis patients and they showed that CIMT was significantly higher than the control group [12]. Another study including 103 systemic lupus erythematosus (SLE) patients and 30 healthy controls demonstrated that increased CIMT was more frequent in patients with SLE [13]. Increased age and inflammation both play a central role in accelerated atherosclerosis, which in turn may be responsible for increased cardiovascular mortality.

Arterial stiffness is an independent predictor of cardiovascular risk. Therefore, measuring arterial stiffness using PWV and AI may provide further information in addition to traditional risk factors [14,15]. Booth at al., reported that arterial stiffness was higher in patients with active AAV than healthy controls by measuring PWV and pulse waveforms [9]. Moreover, they also demonstrated that arterial stiffness was positively correlated with CRP but not with disease duration, ANCA status or the total dose of steroids. Arterial stiffness in patients with remission was similar to controls. Therefore, arterial stiffness appears to be associated with active inflammation. In our study we also found that arterial stiffness was similar in patients in remission and healthy controls.

In the present study, correlation analysis showed that CIMT was positively correlated with age and PWV. A recent review demonstrated that there was a linear relation between CIMT and age in healthy population, suggesting that CIMT progresses linearly with older age [16]. Similar findings between CIMT and age are also supported with several studies [17,18]. Although, PWV was similar between the two groups, it was correlated with CIMT which shows early atherosclerosis. The lack of a difference between AAV patients and controls regarding PWV values was probably due to the fact that the vast majority of our patients were in remission. The positive correlation between CIMT and PWV supports the notion that PWV is indeed an indicator of cardiovascular risk. Also, it is well defined in the literature that increased arterial stiffness is associated with accelerated atherosclerosis in patients with primary systemic vasculitis patients [19,20].

Previous studies have shown classic cardiovascular risk factors such as hypertension and dyslipidemia to be more common in AAV [21,22]. Non-traditional risk factors such as chronic

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vascular inflammation may also lead to endothelial dysfunction resulting in accelerated atherosclerosis in these patients [23]. In our study, although, most of the patients were in remission, CRP levels were still significantly higher than controls. However, we did not find an association between CRP, CIMT or arterial stiffness. This could be due to the low patient number or the fact that the majority of our patients were in remission. However, CRP is a risk factor for atherosclerosis and may very well be another link between inflammation and accelerated atherosclerosis in vasculitis [24].

The association between steroids and CIMT measurements reveal conflicting results in patients with AAV. While some data suggest that steroids may accelerate atherogenesis in AAV patients, other studies do not support this finding [25]. There is no data in the literature regarding the relationship between immunosuppressives other than steroids and CIMT in AAV patients. Some studies suggest that rituximab may decrease CIMT in rheumatoid arthritis patients [26]. According to another study involving 82 lupus nephritis patients, there were no associations between CIMT and the cumulative dose or duration of steroids, hydroxychloroquine, azathioprine, mycophenolic acid and cyclophosphamide [27].

The major study limitations were cross-sectional design and small sample size. There was no prospective follow-up of cardiovascular events. Immunosuppressive use including steroids was another confounding factor. Lastly, we were unable to evaluate the effect of active disease on aortic stiffness, CIMT or other traditional parameters since the majority of our AAV patients were in remission.

Conclusion

The present study showed that CIMT is significantly increased and correlated with age and PWV in patients with AAV compared to controls. CIMT can be used as a screening tool as part of patient follow-up to identify patients at cardiac risk.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University, School of Medicine, Clinical Research Ethics Committee (date/no: 2018/09.2018.653).

All participants gave written informed consent.

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Conflict of interest : The authors declare that there is no conflict of interest.

Authors' contributions: TNI, EA: Concept, TNI, EA: Design, TNI, DBA, HA, DA, CI, AV, HA, FAO, HD, ST, EA: Supervision, TNI, HA, DA, EA: Materials, TNI, DBA, HA, DA, EA: Data collection and /or processing, TNI, DBA, HA, CI, AV, HA, EA: Analysis and/or interpretation, TNI, DBA, HA, DA, CI, AV, HA, FAO, HD, ST, EA: Literature search, TNI, DBA, HA, EA: Writing, TNI, DBA, HA, DA, CI, AV, HA, FAO, HD, ST, EA: Critical Reviews. All authors read and approved the final version of the manuscript.

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The utility of biomarkers to predict steroid response in idiopathic nephrotic syndrome

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ABSTRACT

Objective: The most common form of nephrotic syndrome (NS) is minimal change disease (MCD) in children and focal segmental glomerulosclerosis (FSGS) following it. As, it is important to predict corticosteroid (CS) response at the beginning of the disease, we aimed to evaluate the efficacy of some biomarkers in terms of predicting steroid response in patients with NS.

Patients and Methods: Twenty patients who met the inclusion criteria for the study were divided into 3 groups and 6 healthy control participants were included in the analysis as the 4th group. Group-1 included 10 patients at the first episode of idiopathic NS (INS), group-2 included the same 10 patients in remission, group-3 included 10 patients with steroid resistant NS (SRNS) diagnosed as FSGS by renal biopsy, and group-4 included six healthy children as controls. Urinary and serum cluster of differentiation (CD) CD80, IL-17, IL-23, IL-10, TGF-β, CD86, CD28, CTLA-4 levels were measured for all groups.

Results: Urinary CD80 level in INS-relapse group was significantly higher than the levels of the INS-remission, FSGS and control groups ($p<0.001$). Urinary CD28 and uIL-10 were significantly increased in INS-remission group than INS-relapse ($p<0.05$, $p<0.001$). Serum IL-17 was significantly higher in INS-relapse group than in INS-remission group ($p<0.01$). There was no difference in IL-23,TGF-β,CD86 parameters between groups.

Conclusion: In our study, urinary CD80 levels were significantly higher in the relapse group compared to the other groups. When supported by more comprehensive clinical studies, urinary CD80 level may be a good biomarker to predict CS response and to predict in favor of MCD.

Keywords: Biomarkers, CD80, Nephrotic syndrome, Steroid response

1. INTRODUCTION

The most common form of nephrotic syndrome (NS) is minimal change disease (MCD) in children. It is considered that proteinuria is due to a circulating factor secreted by lymphocytes and suggested that MCD is a disorder of T cell function [1, 2]. The second most common type of NS is focal segmental glomerulosclerosis (FSGS) following MCD. Most nephrotic children with MCD respond to corticosteroid (CS) therapy, whereas, those with FSGS are relatively resistant. There is a risk of progression to end-stage renal disease in FSGS and the treatment and prognosis of MCD and FSGS differ considerably. Currently, the gold standard to differentiate MCD and FSGS is renal biopsy. But, this method is invasive and rarely used especially for patients estimated to be MCD with clinical findings and the patients with first episode of NS whose steroid response is unknown. It is very important to identify biomarkers to predict whether patients are likely to respond CS treatment or not as it can guide the physician.

In idiopathic nephrotic syndrome, although, the use of certain biomarkers to assess treatment response is controversial in the literature, cluster of differentiation 80 (CD80) is the one that has been most emphasized. CD80 is found to be expressed by podoyctes in experimental models of glomerular disease associated with NS [3]. It is reported that CD80 is expressed by the podocytes in patients with MCD and urinary CD80 (uCD80) in MCD relapse is higher than patients in MCD remission and other glomerular diseases like FSGS, membranoproliferative glomerulonephritis, IgA nephropathy and membranous nephropathy [4, 5]. The antigen-specific T-cell receptor binds to CD80/CD86 costimulatory molecules expressed on the surface

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of antigen-presenting cells [6]. It acts as a costimulatory molecule through binding to its receptor CD28 on T cells [3]. CD80 is induced in podocytes by circulating cytokines, microbial products or allergens. Th-17 cell is a member of the CD4 effector T-cell family and is an important mediator in inflammatory and autoimmune diseases by T-cell mediated immunity [7]. In normal settings, the inflammatory immunity and CD80 expression is terminated by regulatory cytokines secreted from T regulatory (Treg) cells, Cytotoxic T-Lymphocyte-Associated 4 (CTLA-4), IL-10, and Transforming Growth Factor-β (TGF-β). Patients with MCD exhibited a significant increase in Th-17 number and related cytokines IL-17 and IL-23, as well as an obvious decrease in Treg number and related cytokines CTLA-4, TGF-β and IL-10 [8]. It is proposed that due to Treg dysfunction and impaired regulatory cytokines, podocyte CD80 expression becomes persistent and induces proteinuria [9].

In this study we aimed to assess the clinical utility of serum and urinary biomarkers to predict CS response. This is a preliminary study evaluating CD80 and other biomarkers in patients at the first episode of idiopathic NS (INS) before CS therapy.

2. PATIENTS and METHODS

This study is a prospective study including twenty six patients who were admitted to the Division of Pediatric Nephrology between March 2018 and March 2020. The study was approved by the Marmara University, School of Medic

ine Clinical Research Ethics Committee (09-2014-0018) and written informed consent was obtained before participation. We divided the participants in 4 groups. Group-1 included 10 patients at the first attack of INS, group-2 included the same 10 patients in remission, group-3 included 10 patients with NS resistant to CS therapy and diagnosed as FSGS by renal biopsy, and group-4 included 6 healthy children as controls. The mean age of the patients with INS, FSGS and controls were 4.8±2.2, 14.8±4.6 and 8.7±3.5 years respectively. Serum albumin and urinary protein levels are shown in Table I. Urinary (u) and serum (s) CD80, CD86, CD28, IL-17, IL-23, IL-10, TGF-β, CTLA-4 were measured in blood and urine using a commercially available ELISA kit (Bender MedSystems, Burlingame, CA) for all groups and urinary concentrations were adjusted with urinary creatinine.

Relapse of the NS was defined as the presence of massive proteinuria confirmed by a urine protein/creatinine ratio (up/uc) ≥2 or 24-hour proteinuria ≥40 mg/m²/hour, and a serum albumin of ≤2.5 g/dl during the course of the episode. Complete remission was defined as no proteinuria confirmed by a up/uc ≤0.2 or 24-hour proteinuria ≤4 mg/m²/hour and a serum albumin of >2.5 g/dl. The mean follow up time was 36.2±3.73 months and the mean relapse rate in patients with INS was 0.7±0.56 per year. All of the patients with INS who had relapses, progressed into remission with CS treatment. These patients were evaluated as steroid sensitive NS (SSNS). Corticosteroid resistance, which means steroid resistant NS (SRNS), was not observed in any patient during follow-up. These findings strongly suggest that these patients with INS are most likely MCDs.

Table I. *Characteristic of Patients with INS, FSGS, Control Subjects*

	Age (years)	Gender	Serum albumin (gr/dl)	24 hour proteinuria (mg/m²/hour)	up/uc ratio
INS in attack					
1	9.9	M	2.3	140	9.8
2	3.4	M	1.6	56	7.4
3	4.6	F	1.32	210	12.6
4	7.1	M	2.3	42	8.7
5	5.6	M	1.5	389	11.8
6	4.1	M	1.4	166	7.5
7	2.8	M	1.45	-	18.7
8	4	M	1.48	62	13.5
9	4.4	M	1.5	243	12.3
10	2	M	1.7	-	9.2
Mean	4.8±2.2		1.65±0.35	163.5±121.25	11.15±3.42
INS in remission					
1	9.9	M	4.6	2.7	0.08
2	3.4	M	3	2.4	0.12
3	4.6	F	4.28	3.6	0.07
4	7.1	M	4.5	1.5	0.13
5	5.6	M	4.39	4.2	0.11
6	4.1	M	3.2	1.84	0.07
7	2.8	M	3.2	-	0.2
8	4	M	4.4	2.5	0.1
9	4.4	M	4	3	0.08
10	2	M	3.5	-	0.02
Mean	4.8±2.2		3.9±0.61	2.71±1.34	0.098±0.04
FSGS					
11	20.2	F	3.4	128	14.3
12	19.5	F	4.1	35	1.6
13	14.8	M	4.2	38	1.4
14	14.8	M	4.6	42	1.5
15	17.4	F	4.6	29	1.1
16	15.8	M	4.4	33	0.2
17	9.2	M	4.6	48	0.18
18	17.1	F	4.6	47	0.17
19	14.3	M	4.4	38	1.7
20	10.9	F	4.8	55	0.15
Mean	14.8±4.6		4.37±0.4	49.3±28.72	4.03±3.69
Control					
21	9.7	F		Neg	
22	13.9	M		Neg	
23	10.1	F		Neg	
24	11.4	M		Neg	
25	5	F		Neg	
26	7.33	M		Neg	
Mean	8.7±3.5				

INS: Idiopathic nephrotic syndrome, up: Urinary protein, uc: Urinary creatinine, FSGS: Focal segmental glomerulosclerosis

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Statistical Analysis

We conducted statistical analysis using SPSS, parametric T test was used for CD80 with homogeneous distribution and non parametric ANOVA (Kruskal-Wallis test) for other parameters because of the non homogeneous distribution and we determined differences between medians using Dunn's comparisons test. A p value < 0.05 was considered significant.

3. RESULTS

Urinary CD80 excretion was significantly elevated in group-1 (INS-relapse) than in group-2 (INS-remission, (p<0.001), group-3 (FSGS, (p<0.001) and group-4 (control, (p<0.001) (Table II and Figure 1). There was no statistically difference in uCD80 excretion between the INS-remission and FSGS groups and also between the control group (Table II). In contrast with the urinary findings, sCD80 concentrations were not different among patients in 4 groups (Table III). Urinary CD28 and uIL-10 were significantly increased in INS-remission group compared to INS-relapse group (p<0.05, p<0.001). There was no difference between groups for other urinary parameters (Table II). Serum IL-17 was significantly higher in INS-relapse than in INS-remission (p<0.01). Serum CTLA-4 was significantly higher in FSGS group than in INS-remission group, but not higher than control group causing a nonsense relation. There was no difference in serum and urinary IL-23, TGF-β, CD86 and urinary CTLA-4 between groups (Table III).

Table II. *Urine Median Levels of Biomarkers in Study Patients*

	INS in attack	INS in remission	FSGS	Control	P
CD80 (ng/gr)	647.25*	92.92*	96.90*	116.62*	0.0001
CD86 (ng/gr)	49.29	25.16	19.35	17.51	0.0857
CD28 (ng/gr)	0*	1970.20*	663.53	12.27	0.0410
IL-17 (pg/gr)	0	0	0	0	0.160
IL-23 (pg/gr)	49378	4515,3	4522.5	0	0.0673
IL-10 (pg/gr)	0*	1084.8*	130.49	0	0.002
TGF-β (pg/gr)	1124650	0	319331	287471	0.114
CTLA-4 (ng/gr)	19.48	9933.9	5052.5	4118.3	0.072

INS: Idiopathic nephrotic syndrome, FSGS: Focal segmental glomerulosclerosis
**groups which the statistical difference is derived from*

Table III. *Serum Median Levels of Biomarkers in Study Patients*

	INS in attack	INS in remission	FSGS	Control	P
CD80 (ng/ml)	0.5050	0.3060	0.3360	0.62	0.05
CD86 (ng/ml)	0.1005	0.68	0.0310	0.058	0.4306
CD28 (ng/ml)	0	0	0.714	0.72	0.2172
IL-17 (pg/ml)	0.2750*	0*	0.042	0.024	0.0093
IL-23 (pg/ml)	32.194	87.939	16.607	38.446	0.2063
IL-10 (pg/ml)	1.718	0.8130	0.4030	0.4020	0.3837
TGF-β (pg/ml)	45273	69462	57116	48156	0.7669
CTLA-4 (ng/ml)	2.64	2.475	8.65	6.37	0.01

INS: Idiopathic nephrotic syndrome, FSGS: Focal segmental glomerulosclerosis
**groups which the statistical difference is derived from*

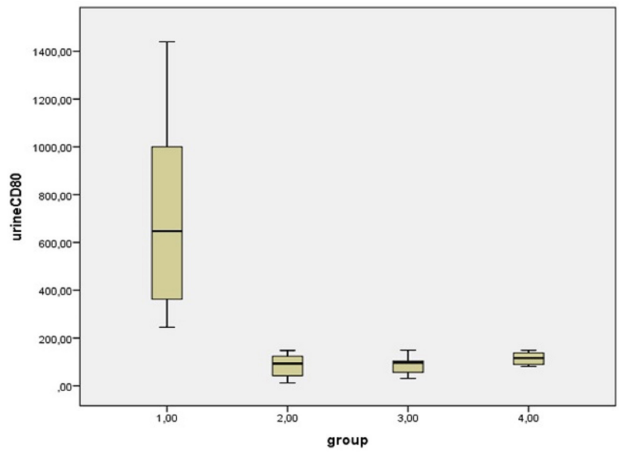

Figure 1*: uCD80 excretion (ng/gr creatinine) in study patients*

4. DISCUSSION

In the current study, CD80 and other biomarkers in patients at the first episode of INS were evaluated in terms of determining the response to steroid treatment. uCD80 levels were found high in patients with SSNS in the first attack, but not in remission and FSGS. This data suggest that uCD80 may be a useful differential marker to distinguish SSNS from SRNS.

Since, steroid response is the most important predictor of prognosis in children with nephrotic syndrome, biomarkers that can be used to predict steroid resistance may be useful in determining prognosis and guiding treatment. A two hit mechanism is accused for T cell disorder: the first hit is CD80 is induced in podocytes by circulating cytokines, microbial products or allergens and the second hit is Treg dysfunction and/or impaired autoregulatory function by the podocyte thus elevated podocyte CD80 expression becomes persistent and induces proteinuria [9]. When human podocytes were incubated with MCD patients' serum in relapse, a significant increase in CD80 expression was found compared to those incubated with MCD patients' serum in remission [10]. But, in another study, no significant upregulation of CD80 was detected in biopsy samples of MCD and FSGS. Also, in the same study, there was no difference in CD80 expression between MCD and FSGS patients in relapse and remission [11]. These conflicting results make it difficult to understand the exact role of CD80 in pathophysiology of NS.

We hypothesize that uCD80 can distinguish MCD from FSGS, as Garin et al., have previously shown. They showed elevated uCD80 levels in pediatric patients with MCD in relapse when compared with MCD in remission, healthy controls and a small number of patients with other glomerular diseases [4,12]. In two other studies, it was also shown that uCD80 was significantly higher in MCD relapse than in FSGS, other glomerulopathies and control groups [5,13]. The increase of uCD80 was found closely associated with relapse of SSNS but was not related to

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the frequency of relapse [14]. When uCD80 was evaluated as a prognostic factor, the patients with high levels of uCD80 showed good response to immunosuppression therapy and decreased rates of chronic kidney disease and then uCD80 expression was thought to be a predictor of good outcome in children with primary NS [15]. However, in another study, uCD80 was elevated in all patients with active kidney disease even in patients with inherited NS and uCD80 was found positively correlated to urinary protein levels. It was stated that uCD80 is unreliable as a differential diagnostic marker between MCD, FSGS and other glomerular diseases [16]. These results are also confusing like the results of studies on CD80 expression in kidney biopsy samples.

In this study, uCD80 levels were found high in patients with SSNS in the first attack, but not in remission and SRNS diagnosed as FSGS. This data suggest that uCD80 may be a useful differential marker to distinguish SSNS from SRNS. However, due to the small number of patients, we could not define a cut-off point for uCD80 level that differentiates SSNS patients from SRNS.

The antigen-specific T-cell receptor binds to CD80/CD86 costimulatory molecules expressed on the surface of antigen-presenting cells [6]. It acts as a costimulatory molecule through binding to its receptors CD28 on T cells [3] . While we expected uCD28 level, like uCD80, to increase at the time of the first attack, urinary CD28 was found to be significantly higher in the remission group than in the relapse group. This was an unexpected result for us. When we searched the literature on this subject, no relevant study was found. To demonstrate the effect of uCD28 if any in the pathogenesis of MCD, prospective well-defined studies are needed.

Treg and Th17 cells are two important subsets of T helper cells. The Th17/Treg balance controls autoimmunity and inflammation and has been found to play an important role in pathogenesis of autoimmune diseases. To assess whether this balance was disturbed in MCD patients, Th-17/Treg balance had been evaluated in 25 new-onset MCD adult patients. Serum Th-17 number, Th-17 related cytokines IL-17 and IL-23 were significantly higher than in the control group and correlated with proteinuria and decreased serum albumin levels [8]. Urinary IL-17 levels were significantly increased in patients with MCD relapse and decreased to baseline with remission [17]. Similarly, in our study sIL-17 levels were significantly higher in relapse group than in remission group confirming the possible relationship of this molecule with physiopathology of SSNS but there was no difference in uIL-17 levels, sIL-23 and uIL-23 levels.

An obvious decrease was observed in serum T-reg number and related cytokines TGF-β and IL-10 in MCD patients in relapse but not in remission [8]. It was shown that the percentages of T-reg cells were similar between patients with MCD in relapse, remission and controls but in relapse group T-reg cells had an impaired ability to suppress T-eff cell proliferation [9,18]. When uTGF-β levels were compared between MCD and FSGS, it was significantly higher in FSGS group than in MCD. Urinary TGF-β was also evaluated according to steroid responsiveness and there was no significant difference between SSNS and SRNS patients. The authors indicated that uTGF-β was able to differentiate between FSGS and MCD but was not a biomarker of steroid responsiveness [19]. In a study with 32 SSNS patients, sIL-10 levels showed no significant difference between relapse and remission phase, but sTGF-β levels of relapse phase were significantly lower than those of remission phase or control group, and returned to normal control levels after steroid therapy [20]. We only found a significant decrease in uIL-10 levels in relapse group compared to remission group, dropping hints that uIL-10 may be an important marker in the physiopathology of MCD. There was no difference between groups for urinary and serum TGF-β levels.

A decrease in Treg number and related cytokines CTLA-4, TGF-β and IL-10 were shown in patients with MCD. It is proposed that due to Treg dysfunction and impaired regulatory cytokines, podocyte CD80 expression becomes persistent and induces proteinuria [8,9]. Garin et al., reported urinary CTLA-4 tends to be low, but not significant, in MCD in relapse [4]. In another study evaluating uCD80, urinary CTLA-4 and their relation, uCD80 was increased significantly in MCD relapse as compared to remission and healthy controls, but urinary CTLA-4 excretion was also higher in MCD patients in relapse than in remission and controls. uCD80 was high as expected but urinary CTLA-4 was not low in MCD patients in relapse and no significant correlation was observed between uCD80 and urinary CTLA-4 [21]. In our study, there was no significant difference in serum and urinary CTLA-4 levels between four groups. According to these results, it is considered that CTLA-4 may not have an important role in pathophysiology of NS.

We have some limitations in this study. Renal biopsy for SSNS patients was not performed because of ethical concerns. But the advantage of our study is to have a relatively long follow-up time for newly diagnosed patients. All ten patients in the study group are still being followed-up as steroid sensitive that is more in favour of MCD. Though, the number of patients are limited, the major advantage of this study is that all the patients included were at the first attack of NS before CS therapy. Patients with SSNS followed up in our department were not included in the study. But the major limitation of our study is that for patients with FSGS, we could not get blood and urine samples during the acute phase of first nephrotic syndrome attack. These patients were already followed in our outpatient clinic. The serum albumin in the FSGS group was actually higher and urinary protein excretion was lower than in the attack group. But, even FSGS patients with hypoalbuminemia and massive proteinuria had lower uCD80 levels than patients with SSNS. For patients with FSGS, it would be much more meaningful to take samples when they emerged as the first episode of NS and have not yet received immunosuppressive treatment. For this reason, prospective studies with a larger number of patients presented with first NS attack who thought to be MCD or FSGS should be planned.

Urinary CD80 is elevated in patients with SSNS. It may be a promising biomarker to predict steroid response and it seems

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to have an important role in the pathogenesis of MCD as the leading cause of SSNS.

The study was approved by the Marmara University, School of Medicine Clinical Research Ethics Committee (09-2014-0018) and written informed consent was obtained before participation.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University, School of Medicine Clinical Research Ethics Committee (09-2014-0018) and written informed consent was obtained before participation.

Conflicts of interest: The authors have declared that they have no competing or potential conflicts of interest.

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Incidence and risk factors of radial artery spasm during distal radial angiography

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ABSTRACT

Objective: Radial artery spasm (RAS) is a common complication of radial coronary angiography. Our aim was to assess how different risk factors influence the occurrence of RAS during distal radial coronary angiography.

Patients and Methods: A total of 183 consecutive patients undergoing distal radial angiography at 2 centers were included in our study. RAS was defined clinically. The relationship between the demographic and clinical characteristics of the patients and the development of RAS was evaluated.

Results: Radial artery spasm developed in 23 (12.5%) of the patients. While the female sex ratio was higher in those who developed RAS, the mean age was lower ($p<0.001$). In addition, procedure time, number of punctures, access time and percutaneous coronary intervention (PCI) rate were found to be higher in patients who developed RAS ($p<0.001$). Multivariate logistic regression analysis showed that gender, age, access time and number of punctures were independent predictors. In the ROC analysis, procedure and access times were found to predict RAS.

Conclusion: Among patients who underwent distal radial angiography, RAS was found to be more common in women and younger individuals. In addition, prolonged procedure and access times and a high number of punctures increase the possibility of RAS.

Keywords: Distal radial angiography, Radial artery spasm, Number of punctures, Access time, Procedure time

1. INTRODUCTION

Percutaneous coronary angiography is a procedure for the diagnosis and treatment of coronary artery disease. In the past, the femoral artery was the primary access point for angiography [1]. However, as technology has advanced, alternative access sites such as the radial, distal radial and ulnar arteries have become viable options [2].

In 2017, Kiemeneij documented that cannulation of the radial artery in the anatomical snuffbox (AS) is safe and practical [3]. The AS is a recessed area on the radial side of the wrist that protrudes when the thumb is extended. The distal portion of the radial artery runs deep through the AS [4]. As it extends further distally, it transforms into the deep palmar branch of the radial artery and connects with the lower part of the ulnar artery, creating the deep palmar arch of the hand. In the event of obstruction at the AS site, tissue ischemia is prevented by sustained forward flow in the superficial palmar arch and interconnected collateral vessels [5]. This novel approach has the potential to alleviate some of the disadvantages of traditional radial artery cannulation from multiple perspectives.

Radial artery spasm (RAS) is a complication observed during radial angiography that can cause significant pain to the patient and in some cases lead to an unsuccessful angiography procedure [6]. Previous studies have found the incidence of RAS to be between 6.8-30% [7]. RAS results from the abrupt narrowing of the radial artery, which makes it difficult to advance the catheter and can lead to failure of the procedure [8]. In case of procedure failure, alternative access routes are used, resulting in prolonged angiography time and an increased risk of complications associated with the new access route [9]. Several studies have documented that the risk of RAS may be increased by various factors, including patient demographics, the presence of cardiovascular risk factors, radial artery anatomy, and factors related to the procedure [7,10-12]. To reduce the risk of RAS, the use of vasodilators, calcium channel blockers, sedation and analgesic medications is recommended prior to the procedure [13]. It is also recommended to use hydrophilic wires and smaller diameter catheters and to avoid cold intra-arterial injections [14].

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The aim of our study is to determine the incidence and predictors of radial artery spasm development in patients who underwent coronary angiography via the distal radial artery. We also compared the characteristics of patients who developed RAS and who did not develop RAS.

2. PATIENTS and METHODS

A total of 183 patients from 2 centers who underwent distal radial angiography were included in our study. Patients were consecutively selected between April 2021 and May 2022. Patients were divided into 2 groups according to whether they had radial artery spasm or not. The study excluded patients who met the following criteria: acute ST elevation myocardial infarction, hemodynamic instability, cardiogenic shock, use of catheters other than 6 French, patient refusal, and those aged 75 years and older. Due to the unreliability of the assessment of RAS in elderly patients, we decided not to include people over 75 years of age in the study. The procedures were performed by the same interventional cardiologists in each center. Demographic characteristics such as age, gender, body mass index (BM), hypertension, diabetes, chronic obstructive pulmonary disease, chronic renal failure, heart rate and blood parameters, and a brief medical history were obtained from each patient.

All patients had a palpable arterial pulse on the distal radial pulse. After disinfection with povidone-iodine, the forearm was placed on a soft surface while the wrist was placed in ulnar deviation and partial flexion to facilitate palpation and puncture of the artery. The operator stood on the patient's right side to prepare for puncture of the distal radial artery. The access point was the deep palmar artery between the first and second metacarpal bones. After injecting 2 mL of procaine Hcl under the skin at the entry point, the needle was guided to the site with the strongest pulse. After the arterial puncture, a straight 0.018-inch guidewire was carefully passed through the patient's wrist. A hydrophilic radial 6-French sheath was then inserted into the distal radial artery. All patients received 2500 units of unfractionated heparin (50 IU/kg) and 200 µg nitrate via the sheath. Right and left 6-F Judkins catheters were used for diagnostic angiography. In cases where interventional procedures were required, the choice between 6-F Judkins, EBU or Amplatz guide catheters was made based on the nature of the lesion and the individual characteristics of the patient. Once the procedure was completed, the radial sheath was withdrawn and immediate hemostasis was achieved by compression. Patients were closely monitored and observed for the development of radial artery spasm.

Radial artery spasm was determined clinically, and a clinical diagnosis of RAS was made based on the presence of two or more of the following criteria, or one if the operator had administered a second dose of the antispasmodic [15]:

a. Persistent pain in the forearm, b. Pain response to catheter manipulation, c. Pain reaction to sheath withdrawal, d. Difficult catheter manipulation after compression by the radial artery, e. Resistance when pulling out the sheath.

The study was approved by the Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee (date and number: 10/05/2024 and 59).

Statistical Analysis

The data were analyzed using the statistical program SPSS 25.0 (Armonk, NY: IBM Corp.). The Kolmogorov-Smirnov test was used to determine whether each variable was normally distributed. Continuous variables with normal distribution were defined as mean ± standard deviation. Continuous variables with abnormal distribution were defined as median (interquartile range). The Student's t-test was used for variables with normal distribution and the Mann-Whitney U-test for variables with abnormal distribution. The Chi-square test was used for the comparison of categorical variables. Receiver operating characteristic (ROC) analysis was used to test the ability of procedure time and access time to predict RAS and to determine a cutoff value based on the sum of the highest sensitivity and specificity. Univariate and multivariate analyzes with logistic regression models were performed to identify predictors of RAS. A P value < 0.05 was considered significant.

3. RESULTS

A total of 183 patients, including 155 patients with stable angina pectoris and 28 non-ST elevation acute coronary syndrome patients, were included in our study. The patients were 54 women and 129 men, and their mean age was 58.6 years. Percutaneous coronary intervention (PCI) was performed in 52 patients. RAS developed in 23 (12.5%) of the patients. The female sex ratio was significantly higher in patients who developed RAS (60.9% vs. 25.0%, p<0.001). The mean age was lower in patients who developed RAS (51.2±7.9 vs. 59.8±10.8, p<0.001). In addition, procedure time, access time and number of punctures were higher in patients with RAS (52.7±15.2 vs. 38.9±10.9, p<0.001, 75.4±22.6 vs. 50.1±12.4, p<0.001, 2.69±0.87 vs. 1.63±0.64, p<0.001, respectively) (Figure 1). In addition, the PCI rate was found to be higher in patients who developed RAS (65.2% vs. 23.1%, p<0.001). There was no difference between patient groups in terms of characteristics such as hypertension, diabetes mellitus, chronic renal failure, heart rate, laboratory parameters and BMI. The basic demographic characteristics of the patients are shown in Table I.

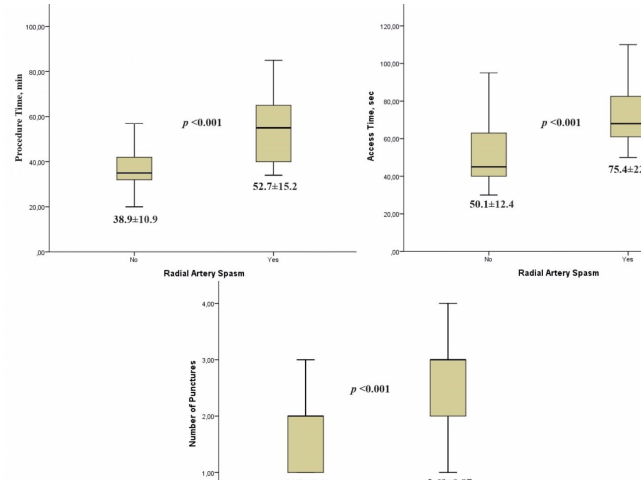

Figure 1. *Comparison of procedure time, access time and number of punctures with box plot in patients with and without radial artery spasm*

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Table I. *Basic demographic characteristics of patients*

	RAS(+) n:23	RAS(-) n:160	P Value
Gender (Female), n(%)	14(60.9)	40(25.0)	**<0.001**
Age, (years)	51.2±7.9	59.8±10.8	**<0.001**
Body mass index, (kg/m2)	28.5±4.3	27.4±3.9	0.184
HT, n(%)	11(47.8)	55(34.4)	0.209
DM, n(%)	8(34.8)	47(29.4)	0.597
COPD n(%)	4(17.4)	24(15.0)	0.766
PCI, n(%)	15(65.2)	37(23.1)	**<0.001**
CRF, n(%)	8(34.8)	47(29.4)	0.597
EF, (%)	50.2±10.3	48.8±10.8	0.567
Heart Rate (minute)	87.0±17.9	85.6±17.2	0.718
Systolic Blood Pressure (mmHg)	134.7±16.6	128.4±17.3	0.104
Diastolic Blood Pressure(mmHg)	80.8±12.3	77.8±11.9	0.256
Procedure time, min	52.7±15.2	38.9±10.9	**<0.001**
Access time, sec	75.4±22.6	50.1±12.4	**<0.001**
Number of punctures	2.69±0.87	1.63±0.64	**<0.001**
Hgb(gr/dl)	13.5±1.8	13.8±1.7	0.450
Hct(%)	41.0±5.1	41.7±5.0	0.524
Plt(10e3/uL)	252±69	250±77	0.932
BUN, (mg/dL)	34(26-44)	37(28-45)	0.712
Creatinine, (mg/dL)	0.87(0.74-1.07)	0.87(0.77-1.02)	0.867

RAS: Radial Artery Spasm, HT: Hypertension, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, PCI: Percutaneous Coronary Intervention, CRF: Chronic Renal Failure, EF: Ejection Fraction, Hgb: Hemoglobin, Hct: Hematocrit, Plt: platelet, BUN: Blood Urea Nitrogen

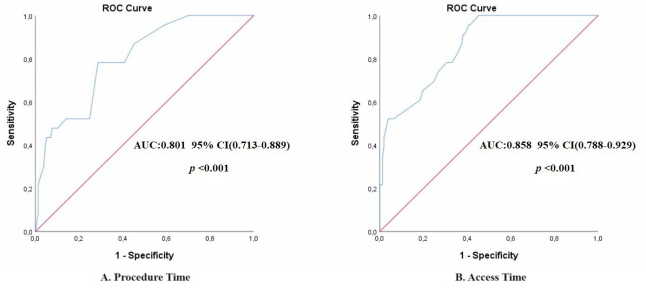

Figure 2. *ROC curve analysis for radial artery spasm prediction using procedure time and access time*

Table II. *Independent determinants of radial artery spasm in univariate and multivariate logistic regression analysis model*

	Univariate analysis			Multivariate analysis		
Radial artery spasm(+)						
	OR	**95%CI**	**p**	**OR**	**95%CI**	**p**
Gender	4.667	1.877-11.601	**0.001**	12.451	1.974-78.527	**0.007**
Age	0.904	0.852-0.959	**0.001**	0.685	0.551-0.852	**0.001**
PCI	6.233	2.451-15.853	**<0.001**	1.469	0.061-35.253	0.813
Procedure time	1.078	1.042-1.114	**<0.001**	1.067	0.952-1.195	0.266
Access time	1.102	1.056-1.150	**<0.001**	1.141	1.036-1.257	**0.007**
Number of punctures	6.514	3.154-13.452	**<0.001**	18.479	2.097-162.842	**0.009**

OR: Odds Ratio, CI: Confident Interval, PCI: Percutaneous Coronary Intervention

Independent predictors of radial artery spasm were determined in univariate and multivariate logistic regression analysis model (Table II). In the univariate analysis, gender (OR:4.667, 95%CI:1.877-11.601, p=0.001), age (OR:0.904, 95%CI:0.852-0.959, p=0.001), PCI (OR:6.233, 95%CI:2.451-15.853, p<0.001), procedure time (OR:1.078, 95%CI:1.042-1.114, p<0.001), access time (OR:1.102, 95%CI:1.056-1.150, p<0.001) and number of punctures (OR:6.514, 95%CI:3.154-13.452, p<0.001) were found to be independent determinants. In the multivariate analysis, gender (OR:12.451, 95%CI:1.974-78.527, p=0.007), age (OR:0.685, 95%CI:0.551-0.852, p=0.001), access time (OR:1.141, 95%CI:1.036-1.257, p=0.007) and number of punctures (OR:18.479, 95%CI:2.097-162.842, p=0.009) were found to be independent determinants. In the ROC analysis, the cutoff value for procedure time of 39.5 predicted radial artery spasm with a sensitivity of 78% and a specificity of 72% [(area under the curve (AUC): 0.801, 95% CI: 0.713-0.889, p<0.001)] (Figure 2A). The cutoff value for access time of 59.0 predicted radial artery spasm with 78% sensitivity and 70% specificity [(area under the curve (AUC): 0.858, 95% CI: 0.788-0.929, p<0.001)] (Figure 2B).

4. DISCUSSION

In our study, 12.5% of patients who underwent coronary angiography via the distal radial artery were found to have radial artery spasm. This was similar to rates reported in the literatüre [7]. We found a higher female gender and PCI rate, lower age, longer procedure and access time, and higher number of punctures in patients who developed RAS.

The use of radial artery access in coronary angiography has come to the fore with low complication rates, high patient satisfaction and rapid recovery times and has become the standard approach in many centers. This method, whose safety and effectiveness has been proven, can provide optimal results with correct patient selection and experienced operators. Some previous studies found distal radial angiography to be superior to the traditional method in terms of patient satisfaction, preservation of radial endothelial functions and preservation of vasomotor functions [16-18]. Another advantage of distal radial angiography is that the process of achieving hemostasis is easier and shorter [19]. Since, the distal radial artery is located closer to the surface on the dorsum of the hand, it requires less pressure for hemostasis. This accelerates the mobilization of patients after the procedure and increases their comfort. Considering all these features, distal radial angiography, which is newer in the radial artery approach, seems to be more advantageous than traditional radial angiography.

The radial artery is a slender blood vessel controlled by alpha-adrenergic nerves. This characteristic makes it prone to spasm, which ultimately leads to the potential failure of medical interventions on this artery [20]. Radial artery spasm is a potential problem associated with the transradial approach and has the potential to impact the procedure at different points. If it occurs at the beginning of coronary angiography, it has the potential to impede the course of the exchange wire. If it occurs in the middle of the procedure, it can cause problems with catheter insertion

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and manipulation. If it occurs at the end of the procedure, it may cause difficulties when trying to withdraw the catheter and sheath. RAS can cause a vasovagal reaction in patients due to the severe pain it causes. It can also lead to procedural delays and, in certain cases, the inability to complete the procedure.

In our study, RAS was found to be more common in women. This situation was consistent with the literatüre [7,10,21]. Mong et al., found that women had greater sensitivity to vasoconstrictors and less sensitivity to vasodilators in their radial arteries compared to men [22]. Furthermore, the smaller size of the radial arteries in women affects the radial artery/sheath ratio, which increases the risk of RAS [7]. As a result of these considerations, some operators opt to initiate the procedure in female patients with smaller diameter catheters. In addition, one of the most important findings of this study is the relationship between patient age and the risk of RAS. Our study shows that younger patients are more prone to RAS during distal radial angiography. The lower prevalence of RAS in the elderly may be due to the physiologic changes associated with aging, including muscle denervation and endothelial dysfunction [8]. However, while some studies support our findings, others, on the contrary, have found a higher rate of RAS in elderly patients [7,8,23]. Therefore, further studies are needed to validate the nature of this association. We also identified procedure time, number of punctures and access time as potential factors contributing to RAS. Our results confirm previous studies [15,24,25]. The first unsuccessful attempt to cannulate the radial artery and subsequent multiple attempts may induce radial artery spasm, which is likely due to muscle structure [26,27]. Longer procedure and access times have the potential to increase RAS by causing more catheter manipulations and more pain.

Healthcare providers should be mindful of these factors and work to facilitate access process and ensure minimal trauma to the radial artery. In light of these findings, healthcare practitioners should consider tailoring their approach to distal radial angiography, taking into account the patient's gender and age, procedure and access times, number of punctures, and potential need for PCI. Preventive measures to reduce RAS, such as smaller diameter catheters or vasodilators, can be used in high-risk situations.

Limitation

Our study included a relatively small number of patients. Some variables that could influence the results (e.g. nutritional status, anxiety level) were not taken into account. The patients' previous experience with angiography or similar procedures was not assessed.

Conclusion

Our study shows that the development of radial artery spasm in patients undergoing distal radial angiography depends on some clinical factors. A closer examination of these factors may help to treat patients better and prevent this complication. Considering these risk factors when cannulating the radial artery may contribute to clinical practice to achieve better outcomes.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee (date and number: 10/05/2024 and 59).

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Conflict of interest: The authors declare that they have no potential conflict of interest regarding the investigation, authorship, and/or publication of this article.

Authors contributions: RK: Study design, Data collection, Statistical data analysis, Literature search, Writing the first draft of the manuscript, TG and MD: Data collection, Writing the first draft of the manuscript, Supervision and quality control. All authors read and approved the final version of the article.

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Mesenteric panniculitis: Prevalence, imaging findings, relation with malignancy, comparison with control group and six-year follow-up

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ABSTRACT

Objective: To investigate the prevalence of mesenteric panniculitis (MP), imaging findings, its relationship with malignancy, development of malignancy in follow-up and make a comparison with the control group.

Patients and Methods: A total of 3196 multidetector computed tomography (CT) scans were evaluated retrospectively in terms of MP. CT findings of MP, accompanying benign and malignant pathologies were examined. Two consecutive patients who matched by age, gender, and abdominal diameter were included in the control group. A comparison was made between the MP and control groups concerning malignancy and new malignancy development during a six-year follow-up.

Results: One hundred and sixty-three MP cases and 326 control cases were included to the study. The most common CT findings of MP were increased density of mesenteric fat, pseudomass appearance, and lymph nodes within the pseudomass. 59.5% (n: 97) of the MP group and 58.3% (n: 190) of the control group were associated with malignancy (p: 0.77). The most common malignancies were colorectal cancer (n: 21, 12.2%) in the MP group, and lung cancer (n: 40, 12.2%) in the control group. During follow-up, new malignancies were detected 9.2% (n: 11) in the MP group and 6.3% (n: 8) in the control group (p: 0.37). Lung cancer (n: 3, 27.3%) in the MP group and colorectal cancer (n: 2, 25%) in the control group were the most frequently seen cancer type (p: 0.09).

Conclusion: Mesenteric panniculitis prevalence is 5.1%. When the MP group was compared with the control group, there was no significant accompanying malignancy and no significant new cancer development was observed.

Keywords: Abdomen, Body CT, Follow-up, Mesenteric panniculitis, Oncologic imaging

1. INTRODUCTION

Mesenteric panniculitis (MP) is an idiopathic chronic nonspecific inflammation of intestinal mesenteric fatty tissue [1, 2]. It is frequently detected incidentally on multidedector computed tomography (CT) examinations [3]. Prevalence is between 0.16% and 7.83% [1-5]. It is frequently seen in the middle and late adulthood and is more frequent in males [4].

As a result of the increased number of abdominal CT scans, specific CT findings of MP were identified and diagnostic frequency was increased [2, 6]. Some studies have shown an association between MP and malignancy, and the incidence of accompanying malignancy has been reported as 17-69.4% [4, 7-12]. It has also been suggested that MP may occur due to or in association with abdominal trauma, autoimmune diseases, mesenteric ischemic disease, granulomatous diseases, infectious and inflammatory diseases, paraneoplastic conditions, and recent surgical procedures [1, 4, 6, 8, 13]. Although, the probabilty of malignancy development in MP cases was reported in the follow up, this relationship is still being questioned [2, 4, 7, 8, 10, 14]. MP is often asymptomatic, usually a benign and self-limited condition. In the literature, the number of MP studies that include follow-up and control groups are very limited [1-3]. In this study, we retrospectively reviewed the multidetector CTs to determine the MP prevalence, imaging findings, comparing the relationship between MP and malignancy with the non-MP control group, and examine the development of new malignancies in the up to 6 years follow-up.

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2. PATIENTS and METHODS

Patients

Our study was approved by the Ethics Committee of Trakya University Hospital (approval number and date: 12/01, 02/07/2018). Multidector CT scans of 3196 patients between January and July of 2012 over 18 years of age, were retrospectively evaluated (MG). The CT findings of MP which are (a) a high attenuation of fat in the mesentery of the small intestine; (b) a pseudomass appearance that slightly displaces but does not invade the neighbouring structures; (c) a pseudocapsule in the form of a dense line that separates the high attenuated mesenteric fat and normal mesentery; (d) short axis <10mm lymph nodes in the pseudomass, and (e) hypodense halos around the vessels and lymph nodes were examined [5]. MP was diagnosed in the presence of at least 3 of 5 CT findings (Fig. 1). Subsequently, cases were reevaluated in terms of MP criteria and exclusion criteria (MG and EY, 13 years of abdominal imaging experience). Mesenteric infiltration (cirrhosis, pancreatitis), mesenteric fibrosis and retention, neoplasia including mesenteric tissue, mesenteric edema, massive ascites, hemorrhage (due to trauma or surgery which occurred during the <6 month period) and mesenteric ischemia were exclusion criteria. After every patient who were included in the MP group, 2 consecutive patients of appropriate gender, age (± 2 years), abdominal diameters measured at umbilical level (± 2cm) and with no MP findings were included in the control group.

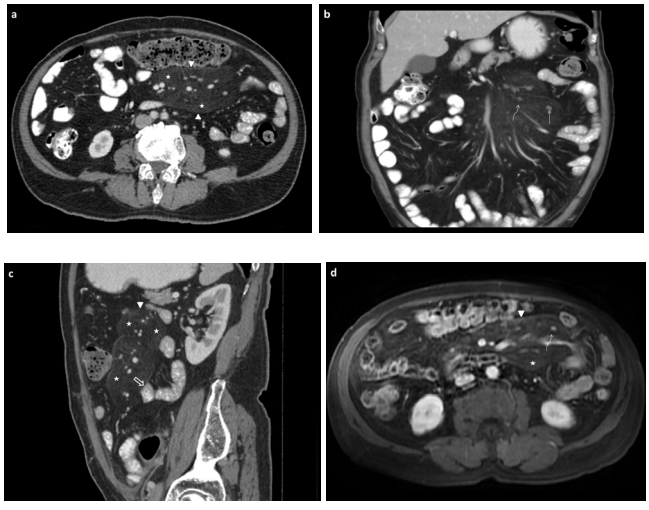

Figure 1. *A 71-year old male patient with prostate and colon cancer. a-c. Typical CT findings of mesenteric panniculitis on axial (a), coronal (b), and sagital (c) views. A pseudomass appearance that slightly displaces but does not invade the neighbouring structures (thick arrow); a pseudocapsule (arrowhead) in the form of a dense line that separates the high attenuated mesenteric fat (asterisk) and normal mesentery; short axis <10mm lymph nodes (thin arrow) in the pseudomass, and hypodense halo (curved arrow) around the vessels and lymph nodes. d. Contrast-enhanced axial MR imaging apearance of mesenteric panniculitis.*

Imaging protocol

Computed tomography studies were performed with a 64-slice scanner (Aquillon, 64-detector, Toshiba Medical Systems, Tokyo, Japan). 300 mg I/mL iohexol (Omnipaque 300; GE Healthcare, Cork, Ireland) were used based on arterial and portal venous phase. Oral contrast solutions 30 ml/1500 ml megluminamidotrizoat (Urovist Angiografin, Schering, Germany) were used 1 hour before the CT scan. The CT parameters were as follows: gantry rotation time, 0.5 s; section collimation, 0.5 mm; helical pitch 53; 125 mAs; and 120 kVp. Images were evaluated at the Picture Archiving Communication Systems (PACS) workstation (Sectra PACS IDS7 17.3, Linköping, Sweden).

Measurements

Patients were evaluated for age, sex, history of abdominal surgery, diabetes mellitus, hypertension. MP prevalence was assessed. CT criteria of MP were compared between patients with and without malignancy in the MP group.

Follow-up

We evaluated the changes in density, size and extent of mesentery (stable, increase, decrease) in MP findings on follow-up CTs in up to 6 years. Imaging findings and medical records were evaluated during the follow-up period. MP group and control group were compared in terms of development of new malignancy and metastasis. In patients with MP who had magnetic resonance (MR) imaging, MR imaging findings of MP were evaluated. Mortality in the MP group and in the control group were compared in the follow-up period.

Statistical analysis

All analyses were performed using the statistical software package SPSS 16.0 for Windows (SPSS Inc. Chicago, IL). The variables were examined using analytic (Kolmogorov–Smirnov or Shapiro–Wilk's test) and visual (histogram) methods by defining whether they are normally distributed. Categorical variables were expressed as percentages and continuous variables were expressed as mean±standard deviation. In intergroup comparisons of continuous variables, the Mann-Whitney U test was used, and for categorical variables chi-square test was used. $p<0.05$ was accepted as the level of significance. An overall 5% type I error level was used to infer statistical significance.

3. RESULTS

Three thousand one hundred and ninety-six consecutive CTs were examined. At the initial assessment, 190 MP patients were detected by a single radiologist (MG). 163 patients (5.1%) were identified and twenty-seven patients were excluded from the study (MG, EY) as a result of the re-evaluation, considering CT criteria and exclusion criteria. Patients with 3 MP findings (n: 6, 3.7%), 4 findings (n: 42, 25.8%) and 5 findings (n: 115, 70.5%) on CT scans were included in the MP group.

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High attenuation of fat in the mesentery root of the small intestine, pseudomass appearance and lymph nodes with <10 mm short axis in pseudomass, were seen in all patients. Pseudocapsule was found in 156 patients (95.7%) and fat halo sign in 116 patients (71.2%).

Male gender was greater in the MP group (90M, 73F), the mean age was 62 ± 11 (range 27-91). Three hundred and twenty-six patients were in the control group (180M, 146F) and the mean age was 60 ± 9 years.

Most of the CTs were performed for a known malignancy, suspicion of malignancy and follow-up (MP group: 115, [70.5%]; control group 190 [58.3%], p: 0.06). Other indications were abdominal pain (MP group: 25, [15.3%]; control group 72, [22%], p: 0.47), others (renal stone, infection, ischemia, etc.) (MP group: 23, [14.1%]; control group 64, [19.6%], p: 0.65).

Malignancy and MP

In the MP group, 97 (59.5%) of 163 patients already had known malignancies. The most common malignancy associated with MP was colorectal cancer (n: 21, 21.4%). Breast (n: 13, 13.2%) and lung (n: 13, 13.2%) cancers were the other most common types of cancer. There were two malignancies in 4 patients. 23 (14.1%) patients with malignancy had viseral metastasis. There was no statistically significant difference in malignancy between the MP group (59.5%) and the control group (58.3%) (p: 0.77) (Table I).

There were no differences in terms of CT criteria between patients with malignancy and those without malignancy in the MP group. In all patients, high attenuation of fat in the mesentery root of the small intestine, pseudomass appearance and lymph nodes were seen with and without malignancy. Pseudocapsule was seen in 92 of patients with malignancy (93.9%) and 64 of patients without malignancy (98.5%) (p: 0.15). Fat halo sign was seen in 71 of patients with malignancy (72.4%) and 45 of patients without malignancy (69,2%) (p: 0.65).

Relationship between MP and other diseases

There was no significant difference between the MP and the control group in terms of comorbidity of the patients. Hypertension (MP group: n: 24, [14.7%]; control group: n: 52, [15.9%], p: 0.66), and diabetes (MP group: n: 12, [7.4%]; control group: n: 27, [8.3%], p: 0.72) were the the most frequently seen comorbidities.

6-year follow-up

In the MP group, 139 patients (85.3%) had clinical and CT follow-up (median 21 months, min-max: 2-72 months). New malignancies were diagnosed in 11 patients (7.9%). The most common malignancies were lung cancer (n: 3) and melanoma (n: 2). New metastases were seen in 25 patients (15.33%). The most common metastases were liver (n: 10) and lung (n: 6). There was no statistically significant difference between the MP group and the control group during follow-up (p: 0.37).

Table I. *Malignancy prevalence of the MP group and the control group*

	MP Group (n:163)	Control Group (n:326)	P value
Type of malignancy, n (%)	97 (59.5%)	190 (58.3%)	0.77
Colorectal	21 (21.4%)	36 (18.9%)	0.45
Breast	13 (13.2%)	25 (13.1%)	0.77
Lung	13 (13.2%)	40 (21%)	0.07
Gynecological	12 (?%)	10 (5.3%)	0.08
Bladder	7 (7.1%)	21 (11%)	0.35
Prostate	7 (7.1%)	3 (1.6%)	0.02
Sarcoma	6 (6.1%)	7 (3.7%)	0.73
Oeso-gastric	5 (5.1%)	9 (4.7%)	0.34
Renal cell cancer	4 (4.1%)	12 (6.3%)	0.65
Lymphoma/Leukemia	4 (4.1%)	4 (2.1%)	0.61
Larynx	3 (3.1%)	6 (3.1 %)	0,96
Seminoma	2 (2.1 %)	3 (1.6%)	0.49
Pancreas	1 (1%)	1 (0.5%)	0.16
Thyroid	1 (1%)	6 (3.1%)	0.26
Nasopharenx	1 (1%)	0 (0%)	0.25
Melanoma	1 (1%)	2 (1%)	0.33
Hepatobiliary	0 (0%)	5 (2.6%)	0.07
Metastasis, n (%)	23 (14.1%)	54 (16.6%)	0.47
Bone	8 (4.9%)	16 (4.9%)	0.17
Lymph node	7 (4.3%)	12 (3.6%)	0.28
Liver	5 (3.1%)	18 (5.5%)	0.26
Lung	2 (1.2%)	18 (5.5%)	0.06
Intraabdominal implant	1 (0.6%)	0 (0%)	0.87
Surrenal	1 (0.6%)	3 (0.9%)	0.82
Brain	1 (0.6%)	1 (0.3%)	0.76

MP: Mesenteric panniculitis

In the control group, 276 patients (84.7%) had follow-up (median 17 months, min-max: 1-72 months). New malignancies were detected in 8 patients (2.9%). These were the colorectal (n: 2), thyroid, larynx, breast, lung, gynecologic, and esophago-gastric cancer (n: 1, each). In 42 patients (15.2%), new metastasis were diagnosed. The most common metastases were in the lung (n:22), the bone (n:12), and the liver (n:10). There was no statistically significant difference between the MP group and the control group during follow-up (p: 0.08) (Table II).

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Table II. *Follow-up findings of the MP group and control group*

	MP Group (n:139)	Control Group (n:276)	P value
Type of malignancy, n (%)	11 (7.9%)	8 (2.9%)	0.37
Lung cancer	3 (2.1%)	1 (0.3%)	0.25
Melanoma	2 (1.4%)	0 (0%)	0.65
Colorectal cancer	1 (0.7%)	2 (0.7%)	0.68
Oeso-gastric	1 (0.7%)	1 (0.3%)	0.56
Gynecological	1 (0.7%)	1 (0.3%)	0.56
Prostate	1 (0.7%)	0 (0%)	0.46
Hepatobiliary	1 (0.7%)	0 (0%)	0.44
Lymphoma	1 (0.7%)	0 (0%)	0.42
Breast	0 (0%)	1 (0.3%)	0.77
Thyroid	0 (0%)	1 (0.3%)	0.72
Larynx	0 (0%)	1 (0.3%)	0.68
Metastasis, n (%)	25 (17.9%)	42 (15.2%)	0.08
Lung	10 (6.1%)	22 (7.9%)	0.16
Liver	6 (3.7%)	10 (3.6%)	0.07
Bone	4 (2.4%)	12 (4.3%)	0.63
Lymph node	4 (2.4%)	8 (2.8%)	0.45
Intrabdominal implant	4 (2.4%)	0 (0%)	0.06
Surrenal	2 (1.2%)	4 (1.4%)	0.37

MP: Mesenteric panniculitis

In the MP group 112 patients (68.7%) had follow-up with control CT. MP findings were stable in 75 patients (67%). There was an increase in 18 patients (16%) and a decrease in 19 patients (17%) in MP findings (Fig. 2,3). During the follow-up period, 32 patients (19.6%) in the MP group and 99 patients (30.4%) in the control group (p: 0.01) died. Twenty-five patients who died in the MP group had follow-up CT scans and the MP findings in 12 patients were stable (48%), decreased in 10 patients (40%) and increased in 3 patients (12%). The rate of decrease in MP findings was found to be higher in the patients who died than in the whole MP group (40% versus 17%). MR imaging was taken in 34 (30.9%) of the follow-up cases and MP findings could be seen in 31 (91%) on the MR. Four patients with newly developed malignancies in the MP group had MR imaging. 2 of them (endometrium, hepatocellular carcinoma, 50%) were detected by MR imaging. Other patients with malignancies were rectum and lung, and MRs were performed after surgery.

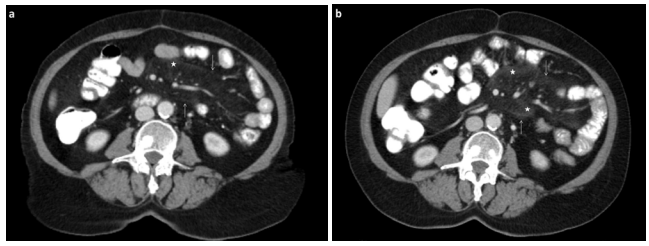

Figure 2. *A 67-year old female patient with breast cancer. Baseline CT (a) and follow-up CT (b) scans demonstrate increased MP findings. Density of mesenteric fat (asterisk) and size of MP increased. Borders of pseudocapsule are more prominent (arrows) when compared with previous CT scan.*

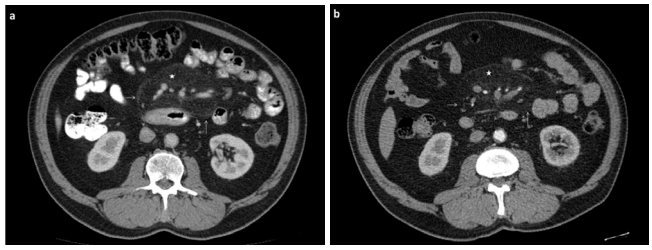

Figure 3. *A 59-year old male patient with lung cancer. Baseline CT (a) and follow-up CT (b) scans demonstrate decreased MP findings. Density of mesenteric fat (asterisk) slightly decreased. Also lateral border of pseudocapsule can not be differentiated clearly (arrow) when comparing with baseline CT scan.*

4. DISCUSSION

As far as we know, our study has the largest number of MP patients, control group, and the longest follow-up period.

In our study, MP prevalence was found as 5.1%. MP was found to be more prevelant in males (90M, 73F) and the mean age was 62 ± 11 (range 27-91). The prevalence of multidetector MP is variable depending on the CT technology, diagnostic criteria, and the method of collecting the patients, ranging from 0.16% to 7.83% [1-5, 8]. Previous studies have found low prevalence such as 0.16% and 0.58%. This result is most probably because of the study methods which is 'keyword search' in terms of patient search [1,8]. Because of the increase of the number of abdominal CT imaging, multidetector CT technical progression, as well as the fact that typical findings of MP have been determined, MP prevalence is increasing as in our study. However, we think that 7.83% of the prevalence in the previous study was due to the small number of the study group [5]. It was found more frequently in middle-aged adult men, although a previous study showed that MP is slightly more common in women [2,4,5].

In our study, a high attenuation of the fat in the mesenteric root, a short axis of <10mm lymph nodes and pseudomass appearance were seen in all patients. There was an increase in MP findings in 18 patients (16.36%) and a decrease in 19 patients (17.27%) with the absence of significant changes in vast majority in MP findings (n: 75, 68.18%). In previous studies, no change

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was observed in the imaging findings of 80.9% of the cases of MP during follow-up [2,4,5,15]. The MP diagnosis was made according to characteristic CT findings [5]. Diseases that can increase the density of the mesenteric fatty tissue can be excluded to enable the diagnosis of MP [2]. Increase of fat density in the mesentery and at least 2 of the other MP criteria are enough for diagnosis. But all CT criteria of MP shoud be carefully evaluated. With these findings, MP may be distinguished from lymphoma, carcinoid tumors, carcinomatosis, primary mesenteric mesothelioma, and mesenteric edema [16,17]. In differential diagnosis, the infiltration of the tumor into the mesenteric fatty tissue is an important exclusion criteria and its presence cannot be diagnosed as MP. The most common CT findings of MP were reported in lymph nodes and in the increased density of the mesenteric fat [3]. Pseudomass appearance, hypodense halo and pseudocapsule appearance are other common findings respectively [2-4].

In our study MP-malignancy association was seen in 97 patients (59.5%). As the mean age of our patients (62 ± 11) was high, comparison was made with the control group that included patients without MP. The frequency of malignancy in the control group was 58.3% and there was no significant difference between groups (p: 0.77). When MP findings are detected, possible accompanying malignancy should be searched for. In the literature, association of malignancy with MP has been reported between 17.6% and 69.3% [1,7]. Excessive prevalence in previous studies may be due to patient selection bias, often involving malignancy and elderly patient populations.

In our study, the most common malignancies associated with MP were colorectal, lung and breast cancer. In the MP group, prostate cancer was significantly higher than in the control group (p: 0.02). Malignancies associated with MP have been shown in literature as colorectal, prostate, lymphoma, melanoma and lung cancer [1-3,5]. In the literature, data about this issue is limited. Further studies are needed to clarify the accompanying malignancy finding and whether it is a coincidental or significant finding.

In our study, there was also no statistically significant difference in new malignancy development compared with the control group (p: 0.37). 11 of 139 patients in the MP group (7.9%) and 8 of 276 patients in the control group (2.9%) were diagnosed with new cancers in the follow up. It has been stated that it is important to follow up the patients with MP for potential development of malignancy. The rate of new malignancy development in previous studies is 4.58-11% [8,9]. In a 5-year follow-up study, new cancer development was found to be statistically significantly higher than the control group [2]. There are also studies showing that there is no significant difference in malignancy development which includes follow-up and control groups [1,3]. However, further prospective studies with larger population are needed.

In our study, 34 patients (30.9%) had MR imaging in the MP group. MP findings were seen in 31 (91.17%) patients, most prominently on fat-suppressed contrast enhanced late phase images. Follow up CT scan has a potential risk of malignity development because of the radiation dose [2]. MP findings can also be detected on MR examination [18,19]. Follow up MR imaging may be considered as an alternative method in MP patients regarding malignancy development. If the breath-holding is not possible, movement artefacts may obscure MP findings.

In our study, there were more deaths in the control group than in the MP group (p: 0.01). In addition, when we analyzed the patients with decreased MP findings, the patients who died had a higher percentage than the entire group (40% versus 17%). These findings may suggest that the presence of MP may lead to a better prognosis in malignant patients and a decrease in MP findings may lead to worse prognosis. We think that these findings should be evaluated in studies with larger patient groups. MP is usually a self-limiting disease with a good prognosis. On the other hand in MP patients with known malignancy, while malignancy is treated, MP is ignored. If malignancy is not accompanied, MP will be ignored again [15]. There was no significant difference about decreased MP findings between patients with malignancy and wihout malignancy [15]. In a recent study, 2 cases with decreased MP findings died in 2 years [3].

Limitations

One of the limitations of our study is retrospective design. Another limitation is that there is no histopathologic verification to confirm MP. However, we think that biopsy is not necessary because of the incidental, self-limiting structure and clear CT findings [2,4,16]. Moreover some of the detected MP patients had no follow-up CT and the mean follow-up time was relatively short. However, we compared the MP group and the control group. As can be understood from the control group, most of our patients are oncology patients. Another limitation was the lack of intra-interobserver variability comparison.

Conclusion

The frequency of MP in our study was 5.1% and the most common accompanying malignancies were colorectal, breast and lung carcinoma. CT findings of MP are usually stable. There was no significant difference regarding accompanying malignancy, development of new malignancy and metastasis between the MP group and the control group. We believe that our findings should be verified with extensive prospective studies including long-term follow up.

Compliance with Ethical Standards

Ethical approval: Our study was approved by the Ethics Committee of Trakya University Hospital (approval number and date: 12/01, 02/07/2018).

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Authors contributions: EY: re-evaluated the MP cases, write the manuscript, performed the statistical analysis and prepared the

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tables and figures, MG: examined the CT studies of the patients. Both authors approved the final manuscript.

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Is aortic elasticity associated with hydration status in stage of chronic renal disease in children?

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ABSTRACT

Objective: We aimed to evaluate cardiovascular risks and influencing factors by measuring aortic elasticity parameters and carotid intima thickness in children with cronic kidney disease (CKD), and also evaluated the hydration status of patients with bioimpedance spectroscopy (BIS) measurements and investigated the effect of hydration status on vascular functions.

Patients and Methods: The study group included an average of 13.3 ± 3.7 years (16 girls and 22 boys, 38 CKD patients), control group on average 12.1 ± 2.9 (16 girls and 15 boys, 31 healthy children). Systolic and diastolic diameters of the aortic annulus and aorta at each level were obtained; z-scores, aortic strain, distensibility, stiffness index were calculated. Carotid intima-media thickness and flow – mediated dilatation were studied. Bioimpedance spectroscopy was performed to all patients.

Results: Interventricular septum and left atrial (p=0.002, p=0.013), sinus valsalva and sinotubular junction z scores (p=0.009, p=0.012) were found to be higher and distensibility and strain decreased, stiffness index increased in the abdominal aorta of patients with CKD (p=0.007, p=0.002, p=0.004). Patients with CKD had statistically significant over-hydration.

Conclusion: Vascular wall changes that affect the elastic properties of the aortic wall begin to develop in childhood in patients with CKD.

Keywords: Chronic kidney disease, Aortic elasticity, Bioimpedance spectroscopy

1.INTRODUCTION

In chronic kidney disease (CKD), cardiovascular mortality and morbidity is higher than in the normal population due to changes in cardiac structure and function. In patients with CKD, left ventricular hypertrophy, dilatation, and systolic and diastolic dysfunction develop in relation to hypertension and volume overload. Many studies have reported that a decrease in aortic elasticity or an increase in aortic stiffness caused cardiovascular side effects and increased mortality in adult patients with CKD [1,2]. Arterial calcification and aortic stiffness have also been reported to be independent predictors of all-cause and cardiovascular mortality in adult CKD patients [3, 4].

The aim of this study was to evaluate cardiovascular risks and influencing factors by measuring parameters of aortic elasticity and carotid intima media thickness in children with CKD. In addition, the hydration status of patients was evaluated with bioimpedance spectroscopy (BIS) measurements and the effect of hydration status on vascular function was investigated.

2. PATIENTS and METHODS

The study group consisted of patients with CKD who were being followed-up at Pediatric Nephrology Outpatient Clinic. The control group consisted of healthy children without

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cardiovascular disease, who were referred to the pediatric cardiology outpatient clinic due to an innocent murmur or non-cardiac chest pain, and who had no cardiac anomaly on echocardiography. Physical examination findings, weight and height measurements, blood pressure and heart rate of all patients were recorded, and body surface area and age-appropriate height and weight percentiles were calculated. In addition, the duration of kidney failure in the patient group and the duration of dialysis in those who underwent dialysis were also recorded. Blood samples were drawn from patients with CKD and evaluated for complete blood count, kidney function tests, electrolytes, and blood gas analysis. Bioimpedance spectroscopy was applied to both the patient and control groups before echocardiography was performed, and the measurements were recorded.

Echocardiography was performed using a Philips Epic 7C echocardiography machine (Release 2.0.1 Philips Healthcare 3000, Minuteman Road, Andover, MA 01810, USA) equipped with 5.2 and 8.3 MHz transducers. All patients underwent M-Mode, two-dimensional and Doppler echocardiographic examinations, and these measurements were obtained using standard techniques according to the recommendations of the American Society of Echocardiography. All measurements were performed by a single investigator and M-Mode z scores were obtained using Detroit Data [5].

•^aSystolic and diastolic diameters of the aortic annulus, the sinus valsalva, the sinotubular junction, the ascending aorta 3 cm distal to the aortic annulus, the proximal aortic arch between truncus brachiocephalicus and left carotid artery, the descending aorta 1 cm distal to the origin of the left subclavian artery, and the abdominal aorta at the level of the diaphragm were measured with two-dimensional echocardiography. Aortic strain, aortic distensibility, and aortic stiffness index was calculated for each subject using the formulas below:

- Aortic strain = (Systolic dimension-Diastolic dimension) / Diastolic dimension
- Aortic stiffness index = logarithm (Systolic blood pressure/ Diastolic blood pressure) / [(Systolic dimension-Diastolic dimension/Diastolic dimension]
- Aortic distensibility = 2 x (Systolic dimension-Diastolic dimension) / [(Systolic blood pressure – Diastolic blood pressure) x Diastolic diameter]

Z-scores of aortic measurements were obtained using Halifax Data [6].

Flow-mediated dilatation of the right brachial artery was performed using an L11 MHz linear array transducer after resting for 10 minutes in the supine position. The straight segment of the brachial artery was identified in the antecubital fossa and basal measurement was made. A pneumatic cuff on the forearm was then inflated to 50 mmHg above systolic blood pressure for 5 minutes. After the cuff was deflated, the brachial artery diameter was measured every 30 seconds in the end-diastolic phase, every three minutes. Flow-mediated dilatation was calculated as the percent change in diameter from baseline to maximum after the cuff was deflated.

Carotid intima-media thickness was measured from the right carotid artery with the patient in the supine position and neck rotated 45° using a Philips IE33 Echocardiography machine (Philips Medical Systems, Bothell, WA, USA) equipped with an 11 MHz linear array probe. The neck vein was found in a section plane and then the transducer was rotated clockwise to a longitudinal plane. Carotid intima-media thickness was measured on the distal wall of the carotid artery. Carotid intima-media thickness was the distance between the two bright lines measured end-to-end. In the electrocardiogram, images of the end-diastolic phase were taken simultaneously with the end of the R wave. Three different measurements were made, and the average value was used.

Measurement of body composition

Bioimpedance spectroscopy was performed with the Body Composition Monitor (BCM) (Fresenius Medical Care GmbH, Bad Homburg, Deutschland). Electrodes were placed on the right hand and foot with the patient in a supine position. All measurements were computed automatically after the patient's height, weight, age, gender and blood pressure data were entered into the monitor. Bioimpedance spectroscopy was applied to dialysis patients before dialysis, non-dialysis patients and control group before echocardiography and other evaluations.

The study was approved by the Marmara University, School of Medicine, Clinical Research Ethics Committee. (date: 4.9.2020, approval number: 1015). All the patients or parents gave written consent for participating in the research.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY, United States of America). Data are presented as mean ± SD for continuous variables and median (range) for non-continuous variables. For comparisons between groups, t-test, $\chi 2$ test, and Mann–Whitney U were used, as appropriate. Correlation between variables was expressed using the Spearman rank correlation coefficient. A p-value <0.05 was considered statistically significant.

3.RESULTS

Patient characteristics

The study group consisted of 38 patients (16 girls, 22 boys) with CKD, between the ages of 6-20 years, with a mean ± SD of 13.3 ± 3.7 (median 14.2) years. The control group consisted of 31 healthy children (16 girls, 15 boys) between the ages of 7-16.5 years, with a mean ± SD of 12.1± 2.92 (median 12.1) years. Duration after diagnosis of CKD in patients ranged between 0.25-17 years (mean ± SD= 5.5 ± 4.05; median: 5 years). Eighteen (47.4%) of the patients with CKD were under renal replacement therapy, nine of whom were on peritoneal dialysis and nine on hemodialysis. The mean±SD duration of dialysis treatment in these patients was 3.5± 2.3 years with a median of 3.25 years.

When the control group and patients with CKD were compared in terms of age, weight, height, and body surface area there

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was no statistically significant difference (Table I). BMI was significantly less in patients compared to the control group (p=0.039). There was no significant difference in terms of systolic blood pressure while the diastolic blood pressure of patients with CKD was higher than the control group (p=0.039).

Table I. *Clinical features of patients*

	Chronic kidney disease(n:38) (mean ± SD)	Control (n:31) (mean ± SD)	P
Age (years)	13.3 ± 3.7	12.1 ± 2.9	0.131
Weight (kg)	39.2 ± 17.3	48.6 ± 22.2	0.061
Height (cm)	141.0± 22.8	148.4± 19.2	0.150
BSA (m^2)	1.2 ± 0.3	1.3± 0.3	0.075
BMI (kg/m^2)	18.6 ± 3.1	20.9 ± 6.3	**0.039**
SBP (mmHg)	117.1± 15.1	112.9± 11.7	0.193
DBP (mmHg)	74.6 ± 12.1	69.0 ± 9.9	**0.039**

BSA:Body surface area, BMI: Body mass index, SBP: Systolic blood pressure, DBP:Diastolic blood pressure

Echocardiographic features of patients

When both groups were compared in terms of echocardiographic parameters, mitral A (p=0.013) and pulmonary velocity (p=0.047), interventricular septum and left atrial z scores (p=0.002 and p=0.013, respectively) were found to be higher in patients with CKD. There was no significant difference between the two groups in terms of isovolumetric relaxation time (IVRT), deceleration time (DT), left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs), left ventricular posterior wall (LVPW), ejection fraction (EF), fractional shortening (FS), or aortic velocity (Table II).

Table II. *Echocardiographic features of patients*

	Chronic kidney disease(n:38) (mean ± SD)	Control (n:31) (mean ± SD)	P
Mitral E (m/sn)	1.0 ± 0.2	1.0 ± 0.1	0.394
Mitral A (m/sn)	0.70± 0.2	0.5 ± 0.1	**0.013**
Mitral E/A	1.5 ± 0.3	1.7 ± 0.3	**0.010**
IVRT (msn)	69.0± 19.1	62.0 ± 13.3	0.081
DT (msn)	125.8± 68.7	144.4 ± 33.4	0.172
IVSd (z scores)	1.66± 1.1	0,8 ± 0.8	**0.002**
LVDd (z scores)	– 0.3 ± 0.9	– 0.1 ± 0.9	0.441
LVDs (z scores)	– 0.6 ± 1.0	– 0.4 ± 1.0	0.334
LVPW (z scores)	1.3 ± 1.0	0.8 ± 0.9	0.055
LA (z scores)	1.3 ±1.0	0.7 ± 1.0	**0.013**
EF(%)	72.1 ± 5.4	71.5 ± 5.2	0.640
FS(%)	41.0 ± 4.5	40.6 ± 4.6	0.729
Aort velocity(m/sn)	1.3 ± 0.2	1.3 ± 0.1	0.408
Pulmonary velocity (m/sn)	1.2 ± 0.2	1.1 ± 0.1	**0.047**

IVRT:Isovolumetric relaxation time, DT: Deceleration time, IVSd: Interventricular septum diastolic diameter, LVDd: Left ventricular diastolic diameter, LVDs: Left ventricular systolic diameter LVPW: Left ventricular posterior wall diameter, LA: Left atrium diameter

Aortic z scores of patients with CKD and control group were compared. Sinus valsalva and sinotubular junction z scores (p=0.009 and p=0.012, respectively) were higher in patients with CKD, while there was no significant difference in ascending, arcus and abdominal aorta diameters (Table III).

Table III. *z scores of aorta*

	Chronic kidney disease(n:38) (mean ± SD)	Control (n:31) (mean ± SD)	P
Anulus	0.1 ± 1.0	0.1 ± 0.8	0.783
Sinus Valsalva	0.6 ± 1.2	– 0.03 ± 0.8	**0.009**
Sinotubuler junction	0.8 ± 1.05	0.2 ± 0.9	**0.001**
Ascending aorta	1.8 ± 1.3	1.02 ± 0.9	0.066
Arcus aorta	0.3 ± 1.1	0.35 ± 1.0	0.766
Abdominal aorta	– 0.32± 1.3	– 0.2 ± 0.9	0.739

Elasticity parameters of aorta

Abdominal aortic distensibility and strain decreased, and stiffness index increased in the patients with CKD compared to the control group (p=0.007, p=0.002 and p=0.004, respectively) indicating that the abdominal aorta was less distensible and stiffer in patients with CKD. There was no difference between the two groups in terms of sinutubular junction, ascending aorta and arcus aorta strain, distensibility, and stiffness index (Table IV).

Table IV. *Aortic elasticity parameters*

	Chronic kidney disease(n:38) (mean ± SD)	Control (n:31) (mean ± SD)	P
Sinus Valsalva			
SI	3.4 ± 0.6	3.60± 0.9	0.350
DIS	5.5 ± 4.1	6.7 ± 11.5	0.568
Strain	6.34± 4.1	7.42 ± 11,71	0.628
Sinutubuler junction			
SI	3.1± 0.8	3.1 ± 0,8	0.991
DIS	8.6 ± 7.2	8.9 ± 8.4	0.875
Strain	9.7 ± 7.1	10.3 ± 9.8	0.784
Ascending aorta			
SI	3.2 ± 0.9	3.3 ± 0,7	0.589
DIS	7.7± 5.9	6.4 ± 5.5	0.329
Strain	9.0 ± 7.0	7.2 ± 6.05	0.253
Arcus aorta			
SI	3.0 ± 0.8	3.1 ± 0.8	0.829
DIS	8.0 ± 5.8	9.3 ± 8.1	0.463
Strain	9.7 ± 6.4	10.4 ± 8.1	0.678
Abdominal aorta			
SI	3.1 ± 0.7	2.6 ± 0.7	**0.004**
DIS	7.60± 6.3	12.2 ± 7.1	**0.007**
Strain	8.6 ± 6.1	14.1 ± 7.6	**0.002**

SI = stiffness index, DIS = distensibility

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Carotid intima-media thickness

There was no statistically significant difference when comparing carotid intima thickness between the patients with CKD and the control group (p=0.490).

Flow-mediated dilatation

Flow-mediated dilatation of the brachial artery was 1.94±0.46 in patients with CKD and 2.30±0.85 in the control group. There was no statistically significant difference between the two groups in terms of flow-mediated dilatation (p=0.490).

Bioimpedance spectroscopy measurements

Patients with CKD had statistically significant over-hydration compared to the control group (p=0.005). The fatty tissue index (p=0.013), fat ratio (p=0.007), and adipose tissue mass (p=0.044) of the patients with CKD were statistically lower than the control group. There was no significant difference between the two groups in terms of other parameters (Table V).

Table V. *Bioimpedance spectroscopy measurements*

	Chronic kidney disease(n:38) (mean ± SD)	Control (n:31) (mean ± SD)	P
Over-hydration (L)	0.6 ± 1.7	– 0.4 ± 1.4	**0.005**
Over-hydration (%)	4.6 ± 11.5	– 1,9 ± 11.0	**0.027**
Urea distribution volume (L)	22.1 ± 9.3	25.9 ± 9.6	0.108
TBW (L)	28.5± 23.5	26.2 ± 9.5	0.596
ECW (L)	9.8 ± 4.0	10.8 ± 3.9	0.309
ICW (L)	13.0 ± 5.6	15.2 ± 5.7	0.127
E/I	0.8± 0.1	0.7 ± 0.05	0.134
LTI (kg/m^2)	14.2 ± 2.4	14.6 ± 2.6	0.469
FTI (kg/m^2)	4.2± 3.0	6.8 ± 5.1	**0.013**
LTM	29.2± 12.7	33.3 ± 11.7	0.180
Fat (kg)	5.7 ± 4.5	11.1 ± 10.4	**0.007**
ATM (kg)	8.9 ± 8.7	15.1 ± 14.2	**0.044**
BCM (kg)	16.8 ± 7.6	19.2± 7.3	0.208

TBW: Total body water, ECW: Extracelluler body water, ICW: Intracelluler body water, E/I: Extracelluler-intracelluler water ratio, LTI: Lean tissue index, FTI: Fatty tissue index, LTM: Lean tissue mass, ATM: Adipose tissue mass, BCM: Body celluler mass

Correlations

Systolic blood pressure positively correlated to total body water (r= 0.366**, p**=0.030), extracellular body water (r= 0.426, p=0.011), intracellular body water (r= 0.404, p=0.016), body mass index (r= 0.560, p=0.016), lean tissue mass (r= 0.370, p=0.029), adipose tissue mass (r= 0.398, p=0.018) and body cellular mass (r= 0.367, p=0.030). No correlation was found between diastolic blood pressure and BIS measurements. In patients with CKD, overhydration was negatively correlated to abdominal aortic stiffness index (SI) (r= – 0.475, p=0.003) and positively correlated with abdominal aorta distensibility (r= 0.363, p=0.027) and strain (r= 0.486, p=0.002).

Diastolic blood pressure positively correlated with interventricular septum diameter (r=0.335, p=0.040), aortic diameter (r=0.291, p=0.015), mitral A velocity (r=0.341, p=0.004) and negatively correlated with abdominal aortic distensibility (r= – 0.255, p=0.015). Additionally, diastolic blood pressure and carotid intima media thickness were positively correlated (r= – 0.386, p=0.017).

In addition, abdominal aorta distensibility negatively correlated with serum urea value (r= – 0.335, p=0.043), and positively correlated with serum calcium levels (r= 0.335, p=0.043), and negatively correlated with serum sodium levels (r= – 0.481, p=0.003).

Ascending aorta SI negatively correlated with HDL (r= – 0.407, p=0.011), LDL (r= – 0.325, p=0.046) and total cholesterol (r= – 0.442, p=0.005).

Ascending aortic distensibility was positively correlated with HDL (r= 0.334, p=0.041), whereas with ascending aortic strain, LDL (r= 0.436, p=0.006) and total cholesterol had positive correlation (r= 0.437, p=0.006).

There was no significant correlation between abdominal aortic stiffness, distensibility and strain with respect to other parameters (Table VI).

Table VI. *Correlation of abdominal aorta stiffness index, distensibility, strain*

	Abdominal aorta SI		Abdominal aorta distensibilty		Abdominal aorta strain	
	r	P	r	P	r	P
Urea	0.228	0.175	**– 0.335**	**0.043**	– 0.319	0.054
Creatinine	0.051	0.762	– 0.066	0.696	– 0.102	0.548
Calcium	– 0.221	0.209	**0.330**	**0.046**	0.298	0.073
Phosphorus	– 0.005	0.974	– 0.107	0.529	– 0.081	0.624
PTH	0.029	0.862	– 0.010	0.954	– 0.038	0.823
SBP	0.111	0.364	0.057	0.640	– 0.089	0.468
DBP	0.070	0.569	– 0.255	0.035	– 0.189	0.121
CKD phase	0.124	0.457	– 0.243	0.142	– 0.208	0.211
CKD duration	– 0.042	0.801	0.008	0.961	0.059	0.724
Dialysis type	– 0.184	0.270	0.115	0.490	0.123	0.461
Dialysis duration	– 0.020	0.993	0.055	0.818	– 0.015	0.951

PTH:Parathormone, SBP: Systolic blood pressure, DBP:Diastolic blood pressure

4. DISCUSSION

Structural arterial changes and accelerated arterial stiffness increase the risk of cardiovascular disease in CKD. Studies in adults have shown that the development of arterial stiffness is associated with increased mortality [1-4, 7-9].

The elastic properties of the great arteries provide the buffering function of the arterial tree. When the buffer capacity of the elastic arteries is reduced, damage to the delicate microcirculatory bed occurs. As arterial stiffness increases, arterial compliance and distensibility decrease. Eventually, increased cardiac afterload causes left ventricular remodeling and hypertrophy. In addition,

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increased arterial stiffness may cause impaired coronary perfusion and myocardial hypoperfusion. As a result, diastolic and systolic left ventricular dysfunction develops [9-14]. In the present study, children with CKD had thicker interventricular septa and larger left atrial diameters, suggesting left ventricular hypertrophy and left ventricular diastolic dysfunction.

Arterial stiffness is the most important parameter that indicates early changes in vascular structures. Studies evaluating the arterial stiffening of patients with CKD were performed in adult patients, and a different technique from ours was used for the measurement of stiffness. Pulse wave velocity measurement from the aorta or its branches has been reported as the gold standard for arterial stiffness [7,9,12]. Therefore, studies in adults have also measured pulse wave velocities of the ascending aorta, aortic arch, common carotid artery, femoral artery, or brachial artery [3,8,14,15]. In the study of Sayın et al., aortic stiffness was calculated by measuring only the diameters of the ascending aorta in systole and diastole [1]. Later, echocardiography was used in the evaluation of aortic elasticity in many studies [16,17]. Arterial stiffness is associated with arterial dilatation and arterial wall hypertrophy [10,18]. For this reason, we hypothesized that dilatation at the level of sinus valsalva and sinotubular junction in children with CKD is a precursor to arterial stiffness. The results of our study suggested that arterial stiffness in CKD begins in childhood and occurs first in the abdominal aorta, and then affects the sinus valsalva and sinotubular junction regions of the aorta. We found that the stiffness index increased, and distensibility and strain decreased in the abdominal aorta in children with CKD. There was no significant difference in the stiffness index, distensibility and strain at the level of sinus valsalva, sinotubular junction, ascending aorta and aortic arch compared to healthy children. However, patients with CKD had higher aorta z scores at the level of sinus valsalva and sinotubular junction.

The mechanism and chronology of the development of arterial stiffness in CKD is not fully understood. Many studies have shown that diabetes, hypertension, obesity and dyslipidemia are risk factors for premature vascular aging in children. Several studies have reported that uremia is an important factor affecting vascular aging. Uremia, mineral bone disease, hypertension, over-hydration, inflammation and oxidative stress all cause significant changes in vascular structure and functions in children with CKD [9-11].

The typical phenotype of uremic arteriopathy is arterial wall hypertrophy, decreased elastin, and arterial calcification. The hallmark of CKD-related arterial disease is vascular calcification in the intima or media layer of the arterial wall [10,11]. Elastic lamellar calcifications and increased calcium content are observed in the arteries of uremic patients. In young patients with CKD, either during predialysis or the dialysis period, medial calcification and accumulation of hydroxyapatite deposits occur within the arterial wall. In addition, hyperphosphatemia also increases osteoblastic activity, induces apoptosis in vascular muscle cells and causes deposition of mineralized apoptotic bodies in the arterial wall [9,10]. There are also significant elastic lamellar calcifications suggesting a potential role of parathyroid hormone [10,15]. In the present study, decreased abdominal aortic elasticity was associated with increased urea level and decreased calcium level in patients with CKD. This suggests that arterial calcification occurs in uremic patients, as reported in previous studies. High urea levels and accumulation of calcium in the vessel wall appear to be the causes of decreased aortic distensibility in pediatric or young adult patients with CKD.

Anecdotally, we had noticed that our patients with CKD had higher diastolic blood pressure, thicker interventricular septum (IVS) and wider left atrium, and high diastolic blood pressure was associated with IVS thickness and left atrial diameter. Furthermore, we found that high diastolic blood pressure was also associated with decreased abdominal aortic distensibility and increased carotid intima-media thickness. Measurement of carotid intima-media thickness in adults is used as a well-defined marker for atherosclerotic status. Adult studies have reported an increase in carotid intima-media thickness in patients with CKD, dialysis patients, and after kidney transplantation [10]. We found no difference in carotid intima-media thickness measurements in pediatric subjects in the present study.

The increase in mitral A velocity and decrease in mitral E/A in our patients with CKD suggested diastolic dysfunction. Left ventricular diastolic dysfunction and left ventricular hypertrophy were also found in previous studies in pediatric CKD patients [8,19-22]. Children with end-stage renal disease and diastolic dysfunction are thought to be at increased risk of ventricular systolic dysfunction, particularly leading to congestive heart failure and premature cardiac death. Arterial stiffening raises myocardial oxygen consumption for a given stroke volume, and ventricular systolic stiffening amplifies this effect. Moreover, arterial stiffening could influence diastole by elevating systolic load to prolong relaxation, compromise filling, and raise end-diastolic pressure. It has been suggested that vascular stiffness tends to increase and may contribute to the pathophysiology of diastolic heart failure [21,23,24].

Bioelectrical impedance analysis is the gold standard method recommended for objective evaluation and monitoring of hydration status [25,26]. Chronic volume overload in CKD patients can induce changes in mechanical forces and lead to changes in the geometry and composition of the vessel walls. Kwan et al., reported that patients with over-hydration were usually asymptomatic, and that bispectral index (BIS) was important in patients on peritoneal dialysis [25]. In this study, over-hydration was associated with high blood pressure and arterial stiffness, and may contribute to increased cardiovascular risk in this group of patients.

In individuals with normal elastic functions, the increased volume causes stretching of the arterial walls, affecting the aortic diameters, resulting in an increase in arterial strain and distensibility and a decrease in the stiffness index. In patients with CKD, on the other hand, elastic functions are impaired and the increased volume increases the pulse pressure without making a difference in aortic diameters due to higher arterial stiffness. This leads to a deterioration in the elastic parameters of the aorta and causes a decrease in arterial strain and distensibility and an increase in the stiffness index [1,25].

The children with CKD in the present study were overhydrated compared to normal children. However, unlike other studies, overhydration did not correlate to diastolic blood pressure, which is related to peripheral vascular resistance rather than volume overload. In the study cohort of patients with CKD, it was observed that, although the abdominal aorta had stiffened, distensibility and strain were decreased. This increased distensibility of the abdominal aorta correlated with over-hydration, indicating a still normal response to increased cardiac output in children and in contrast to earlier reports of studies in adults. This may be due to slowly progressing calcification of vascular wall, which has not reached the degree seen in adult CKD patients.

Conclusion

These results suggest that vascular wall changes effecting the elastic properties of the aortic wall start to develop in childhood in patients with CKD and are related to severity and the hydration status of the patients. Further larger studies are necessary to confirm these findings of vasculopathy in children with CKD. Close monitoring of hydration status in pediatric patients with CKD is also of cardiac importance. We suggest that cardiovascular functions should be monitored and vascular functional parameters should be measured in pediatric patients with CKD in order to recognize cardiovascular complications of CKD early.

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Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University, School of Medicine, Clinical Research Ethics Committee. (date: 4.9.2020, approval number: 1015). All the patients and parents gave written consent for participating in the research.

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Authors contributions: OS**:** Conception, design, data collection and/or processing, analysis and/or interpretation, literature review, writer, SA: Conception, design, data collection and/or processing, EDB: Conception, design, data collection and/or processing, OT: Conception, design, data collection and/or processing, HA: Conception, design, FA : Conception, design, supervision, critical review. All authors approved the final version of the manuscript.

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The impact of vitamin D deficiency on treatment success of cervical interlaminar epidural steroid injection

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ABSTRACT

Objective: Our aim is to investigate the effect of vitamin D deficiency on treatment success of cervical interlaminar epidural steroid injection (ILESI) in patients with cervical disc herniation-related chronic radiculopathy.

Patients and Methods: Fifty patients who had neck and unilateral extremity pain and received cervical ILESI were included. The patients were divided into two groups according to their serum 25 (OH) D levels as Group 1 (>20 ng/mL) and Group 2 (<20 ng/mL). Clinical and demographic data, magnetic resonance imaging (MRI) scans, pre-procedural laboratory tests, and pain scores were recorded. The patients were assessed before procedure and at three and six months after procedure.

Results: Mean serum 25(OH)D level was 29.49±10.9 in Group 1 and 12.06±3.49 in Group 2, indicating a statistically significant difference ($p<0.001$). A significant improvement in pain scores was observed in both groups at six months of follow-up ($p<0.001$). Treatment success rates were significantly lower in vitamin D-deficient group at three months ($p=0.024$), while there was no significant difference between the groups at six months.

Conclusions: Vitamin D level is a factor affecting short-term treatment success in patients undergoing cervical ILESI.

Keywords: Vitamin D deficiency, Cervical radiculopathy, Neck pain, Epidural injection

1. INTRODUCTION

Cervical radicular pain is defined as pain perceived in the upper limb and/or neck caused by irritation or injury of a cervical spine nerve [1] . Its annual incidence varies from 0.83 to 1.79/1,000 adults [2]. The most common causes of cervical radicular pain include cervical disc herniation and/or spinal stenosis. The first-line treatment is conservative with activity modification, medical treatment, physical therapy modalities, and exercises. In unresponsive cases, cervical interlaminar epidural steroid injections (ILESIs) are frequently used as an alternative treatment option before surgey [3].

There are several studies demonstrating that cervical ILESIs are effective and safe in the long-term management of cervical disc herniation-related chronic cervical radiculopathy [3-5]. Success of the treatment depends on various factors such as duration of symptoms, concomitant foraminal and central spinal stenosis, level of disc herniation, presence of possible neuropathic pain components, and coexisting central sensitization; however, there is still an ongoing debate regarding the exact role of aforementioned factors in the etiology of cervical radicular pain, which brings to mind the thought that there may be other clinical parameters that have not been the subject of research in identifying the patient group that would benefit from the treatment [5,6].

25-hydroxy vitamin D (25(OH)D) deficiency is associated with various skeletal disorders and chronic painful conditions [7]. Previous studies have shown that serum vitamin D levels are significantly lower in patients with chronic neck pain [8]. However, the exact physiological mechanism underlying

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vitamin D deficiency-related pain is still unclear. Vitamin D exerts anti-inflammatory effects by reducing the release of proinflammatory cytokines and inhibiting T-cell responses [7]. *In vitro* studies have demonstrated that vitamin D inhibits prostaglandin E2 (PGE2) synthesis [9]. Both observational and interventional studies have suggested that vitamin D plays a key role in the pain intensity and pain management in various clinical settings [10,11]. Therefore, concomitant low vitamin D levels may induce more inflammatory reaction around the spinal nerve root and dorsal root ganglion, implicating in the etiopathogenesis of disc herniation-related radicular pain.

In our knowledge, there is no study investigating the role of 25(OH)D levels on treatment success of ILESIs in patients with cervical disc herniation-related chronic radiculopathy in the literature. In the present study, we hypothesized that vitamin D deficiency could adversely affect the treatment success of ILESIs in this group of patients by increasing the proinflammatory response. We, therefore, aimed to investigate the role of vitamin D levels on treatment success of ILESIs in patients with cervical disc herniation-related chronic radiculopathy.

2. PATIENTS and METHODS

Study Design and Study Population

This single-center, retrospective study was conducted at Pain Management Center of a tertiary care center between January 2020 and January 2021. The patients who had axial neck and unilateral radicular extremity pain for at least three months and were diagnosed with protruded disc herniation by magnetic resonance imaging (MRI) were screened using the hospital database. To acquire a homogeneous group, we searched a total of 312 patients between 18 and 65 years of age who underwent fluoroscopy-guided C7-T1 cervical ILESI. Patients with metabolic diseases (*e.g.*, hyperparathyroidism, hypoparathyroidism, hyperthyroidism, hypothyroidism, diabetes mellitus), having a history of cervical surgery, multilevel disc herniation, cervical spinal stenosis, and/or those with missing MRI, demographic, and clinical data and pre-procedural laboratory tests, including serum 25(OH)D levels were excluded from the study. Finally, a total of 50 patients who met the inclusion criteria were recruited. Clinical and demographic data, symptom duration, serum 25(OH)D levels, pre – and post-injection, three – and six-month Numerical Rating Scale (NRS) pain scores, painkiller use (paracetamol, non-steroidal anti-inflammatory drugs and opioids), chronic disease (disease other than metabolic diseases), and patients who underwent surgery after injection were noted. The patients were divided into two groups according to their serum 25(OH)D levels as Group 1 (>20 ng/mL) and Group 2 (<20 ng/mL). NRS was used for measuring pain intensity. It is expressed between 0 and 10. Zero means no pain, 10 means the most severe pain. A decrease of 50% or more in the NRS pain scores was defined as treatment success in the follow-up.

All patients were informed about the possible diagnostic and therapeutic procedures and a written informed consent was obtained. The study protocol was approved by the Marmara University School of Medicine Clinical Researches Ethics Committee (Date: 12/13/2021 Number: 09.2021.1390). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Injection Technique

The patient was placed in the prone position and cutaneous anesthesia was performed with 3 mL of 2% prilocaine using sterile technique. After imaging the C7-T1 space with fluoroscopy, we entered from the right/left paramedian part of the C7-T1 space with an 18-gauge Tuohy needle, and the C-arm was set in the contralateral oblique position to determine the depth of the needle. Under intermittent fluoroscopic imaging, the needle was advanced, and access to the epidural space was confirmed by the loss of resistance technique. The epidural spread was, then, verified with a contrast agent, and a mixture of 10 mg of dexamethasone, 1 mL of 2% lidocaine hydrochloride, and 1 mL of 0.9% saline was applied to the epidural space. The patient was discharged with recommendations after being kept under observation for 2 hours following the procedure. All injections were performed by a single pain medicine specialist who had at least 10 years of experience.

Statistical Analysis

According to a study by Ozturk et al., based on the relationship between pain and epidural treatment success at the third month the sample size should be 47 to achieve a 95% confidence interval and 90% power [11]. Statistical analysis was performed using the SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or number and frequency, where applicable. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to analyze the normal distribution of quantitative data. For the comparison of non-normally distributed data, the Mann-Whitney U test was used, while the independent t-test was used to compare normally distributed data. The chi-square test was used to measure the inter-group differences in data on treatment success, chronic disease history, use of painkillers, and post-treatment surgical procedures. The changes over time with treatment for non-normally distributed data was determined by Friedman test. A p value of <0.05 was considered statistically significant.

3. RESULTS

Of a total of 50 patients included in the study (Figure 1), 16 were males and 34 were females with a mean age of 48.40 (29-65) years. Group 1 included 24 patients and Group 2 included 26 patients. The mean serum 25(OH)D level was 29.49±10.9 in Group 1 and 12.06±3.49 in Group 2, indicating a statistically significant difference (p<0.001). The ILESI procedure was applied to all patients at the C7–T1 level, and no major complications were observed. There was no significant difference between the two groups in terms of sociodemographic and clinical characteristics such as age, sex, history of chronic diseases, body mass index,

and symptom duration. In addition, there was no significant difference between the two groups in terms of undergoing surgery and painkiller use after treatment (Table I).

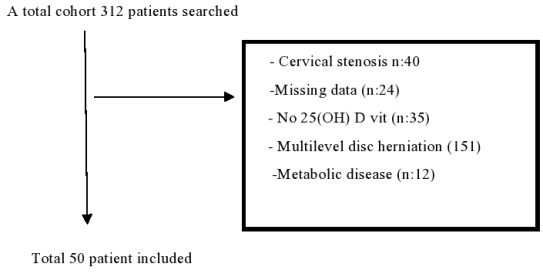

Figure 1. *Flow chart*

The pre-treatment NRS scores of Group 1 and Group 2 were 8.41±1.21 and 8.19±0.98, respectively, indicating no significant difference between the two groups (p>0.05) (Table I). However, at three months, 16 patients (67%) in Group 1 and nine patients (35%) in Group 2 achieved treatment success, indicating a significant difference between the two groups (p=0.024). On the other hand, there was no significant difference in the NRS scores of patients at six months (p>0.05) (Table II). In addition, there was a significant improvement in pain scores in all patients at three and six months compared to pre-treatment scores (Table III).

Table I. *Comparison of demographic and treatment characteristics of the groups*

Variable		Group 1 (n=24)	Group 2 (n=26)	P value
Vitamin D level (ng/mL)*		29.49 ± 10.91	12.06 ±3.49	**< 0.001** *
Age (years)		51.71 ± 10.86	45.35 ± 12.23	0.058 **
BMI (kg/m^2)		25.21 ± 3.39	26.14 ± 3.54	0.257*
Pre-treatment NRS		8.41 ±1.21	8.19 ±0.98	0.321 *
Symptom duration (month)		11 (3 – 48)	10 (3 – 48)	0.452**
Sex	Male	10 (41%)	6 (23%)	
	Female	14 (59%)	20 (77%)	0.159 ***
Chronic diseases	Yes	16 (66%)	7 (27%)	
	No	8 (34%)	19 (73%)	0.050 ***
Painkiller use	Yes	8 (34%)	10 (38%)	
	No	16 (66%)	16 (62%)	0.706 ***
Post-treatment surgery	Yes	1 (4%)	1 (4%)	
	No	23 (96%)	25 (96%)	0.954 ***

*Data are given in mean ± standard deviation or number and %, unless otherwise stated. BMI: body mass index, NRS: Numerical Rating Scale, Group 1: serum 25(OH)D >20 ng/mL, Group 2: serum 25(OH)D <20 ng/mL. *Independent t test; **Mann-Whitney U test; ***Chi-square test.*

Table II. *Comparison of groups in terms of treatment success*

Variable	Group 1 (n=24)	Group 2 (n=26)	P value
Month3			
Yes (n = 25)	16 (67%)	9 (35%)	
			0.024
No (n = 25)	8 (33%)	17(65%)	
Month6			
Yes (n = 19)	9 (38%)	10 (38%)	
			0.944
No (n = 31)	15 (62%)	16 (62%)	

Chi-square test, Group 1: serum 25(OH)D >20 ng/mL, Group 2: serum 25(OH) D <20 ng/mL.

Table III. *Changes in NRS scores over time*

	Mean±SD	P value
Group 1-NRS Pre[1]	8.41 ± 1.21	
Group 1-NRS Month 3[2]	4.00 ± 2.62	<0.001[a]
Group 1-NRS Month 6[3]	5.00 ± 2.52	
Group 2-NRS.Pre[1]	8.19 ± 0.98	
Group 2-NRS Month 3[2]	4.92 ± 3.30	<0.001[b]
Group 2-NRS Month 6[3]	5.42 ± 3.27	
Total NRS Pre[1]	8.30 ± 1.09	
Total NRS Month 3[2]	4.48 ± 3.01	<0.001[c]
Total NRS Month 6[3]	5.22 ± 2.97	

aPost-hoc tests: 1-2, 1-3, 2-3, significant;bPost-hoc tests: 1-2, 1-3, significant ;cPost-hoc tests: 1-2, 1-3, significant;; Pre: before the procedure, Group 1: serum 25(OH)D >20 ng/mL, Group 2: serum 25(OH)D <20 ng/mL. NRS: Numerical Rating Scale.

4. DISCUSSION

In the present study, we investigated the role of vitamin D levels on treatment success of ILESIs in patients with cervical disc herniation-related chronic radiculopathy. Our study results showed that the mean serum 25(OH)D levels were significantly lower in Group 2 than Group 1. Considering a decrease of 50% or more in the NRS pain scores compared to baseline as treatment success, 16 patients (67%) in Group 1 and nine patients (35%) in Group 2 achieved treatment success at three months, indicating a significant difference between the two groups. These findings suggest that low 25(OH)D levels may adversely affect the treatment success of ILESIs in patients with chronic cervical radiculopathy. The lack of a significant difference in the six-month measurements between the groups indicates that these effects are short-term effects in this patient population.

The exact physiological mechanism underlying vitamin D deficiency-related pain has not been elucidated yet. Both animal and clinical studies have demonstrated that vitamin D deficiency affects peripheral and parasympathetic nervous system [12,13]. Besides vitamin D receptors and vitamin D-activating enzymes in the central nervous system, the effects of vitamin D on neurotransmitters have been studied to examine the possible relationship between pain and vitamin D deficiency in patients with fibromyalgia [14]. However, the most

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likely mechanism which explains the role of vitamin D in pain management is associated with its anti-inflammatory effects [7]. In case of vitamin D deficiency, the immune system favors a more inflammatory immune response involving Th1 and Th17 cells rather than Th2 and regulatory T cells (Tregs) [15]. On the contrary, adequate vitamin D levels results in less inflammation and lower levels of inflammatory cytokines and prostaglandins [16]. *In vitro* studies have demonstrated that vitamin D inhibits the PGE2 synthesis in fibroblasts [9]. In a study, vitamin D supplementation decreased musculoskeletal pain and was found to be associated with reduced inflammatory cytokine levels including PGE2 [17]. In the current study, the lower treatment success in the patients with low vitamin D levels in the short term can be attributed to the proinflammatory contribution of low vitamin D level to radiculitis due to cervical disc herniation in these patients.

Although, there are several studies investigating the effects of vitamin D level on postoperative outcomes in patients undergoing spinal surgery, only one study is available in the literature evaluating the role of vitamin D level in the success of interventional pain management [11,18]. In their study, Ozturk et al., investigated the effect of vitamin D deficiency on treatment success of fluoroscopy-guided transforaminal epidural steroid injection in patients with lumbar disc herniation-related chronic radiculopathy [11]. The treatment success was significantly lower in the patients with low vitamin D levels at three weeks and three months of follow-up. Our study included patients with cervical disc herniation-related chronic radicular pain and cervical ILESI was applied. At three months of follow-up, the treatment success was significantly lower in the patients with low vitamin D levels, consistent with the aforementioned study [11]. However, we observed no significant difference in the treatment success at six months between the groups. This can be attributed to the decrease in the long-term anti-inflammatory effect of cervical ILESI in both groups which had comparable pain scores at baseline.

Despite a high number of studies showing that cervical ILESI is effective and safe in the long-term treatment of chronic radiculopathy, consistent with our study findings, debates regarding which parameters are predictive for treatment success still continue [19,20]. In their study, Celenlioglu et al., investigated the predictors of treatment success at six months after cervical ILESI administration and concluded that severe foraminal and central spinal stenosis was the main predictor of poor treatment outcomes [5]. In another study, Oh et al., evaluated predictors of treatment success in the short term (2 to 3 weeks) after cervical ILESI administration [3]. The authors reported that spinal stenosis, prolonged symptom duration, and neuropathic pain were predictors of poor treatment outcomes. Unlike these studies, we excluded patients with foraminal and central spinal stenosis. In addition, we observed no significant difference in the symptom duration between the groups in our study. Also, we were unable to assess neuropathic pain components and central sensitiziation in our study, which may explain the lack of a significant difference in treatment success in the long term in both groups. In the literature, the effect of vitamin D on nociceptive and inflammatory pain are well documented; however, there is a limited number of data regarding its effect on neuropathic pain [17,21].

Nonetheless, there are some limitations to this study. First, the study has a single-center, retrospective design. Second, we were unable to evaluate quality of life and functional status of patients. Third, serum 25(OH)D levels were not high enough to be categorized. On the other hand, a serum 25(OH)D level of 20 ng/mL was defined as vitamin D deficiency, which was significantly lower compared to the other group. This allowed us to evaluate the effect of vitamin D on the treatment success of cervical ILESI. Despite all these limitations, to the best of our knowledge, this is the first study to investigate the effect of vitamin D on treatment success with cervical ILESI. With a specific population and long-term results, we believe that it provides a valuable contribution to the body of knowledge in the literature on this subject.

In conclusion, low serum 25(OH)D level before cervical ILESI administration should be considered a factor which may reduce the treatment success in the short term in patients with cervical disc herniation-related chronic radiculopathy. Therefore, evaluation of serum 25(OH)D levels before the procedure and its replacement, if necessary, may be associated with the increased treatment success after cervical ILESI. However, further large-scale, multi-center, prospective studies are warranted to gain a better understanding of the effect of 25(OH)D on treatment success in this patient population.

Compliance with Ethical Standards

Ethical approval: The study protocol was approved by the Marmara University School of Medicine Clinical Research Ethics Committee (Date: 12/13/2021 Number: 09.2021.1390). All patients were informed about the possible diagnostic and therapeutic procedures and a written informed consent was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Authors contributions: SS: Conceived and designed the analysis, made the research and prepared the original draft, AZD, OA, BD and MA : Collected the study data, RS: Performed data analysis with contributed analysis tool, OHG: Supervisor – reviewed the draft, OHG: Supervisor – reviewed and edited the draft. All authors approved the final version of the article to be published.

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ChatGPT versus strabismus specialist on common questions about strabismus management: a comparative analysis of appropriateness and readability

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ABSTRACT

Objective: Patients widely use artificial intelligence-based chatbots, and this study aims to determine their utility and limitations on questions about strabismus. The answers to the common questions about the management of strabismus provided by Chat Generative Pre-trained Transformer (ChatGPT)-3.5, an artificial intelligence-powered chatbot, were compared to answers from a strabismus specialist (The Specialist) in terms of appropriateness and readability.

Patients and Methods: In this descriptive, cross-sectional study, a list of questions from strabismus patients or caregivers in outpatient clinics about treatment, prognosis, postoperative care, and complications were subjected to ChatGPT and The Specialist. The answers of ChatGPT were classified as appropriate or not, considering the answers of The Specialist as the reference. The readability of all the answers was assessed according to the parameters of the Readable online toolkit.

Results: All answers provided by ChatGPT were classified as appropriate. The mean Flesch Kincaid Grade Levels of the respective answers given by ChatGPT and The Specialist were 13.75±1.55 and 10.17±2.17 ($p<0.001$), higher levels indicating complexity; and the mean Flesch Reading Ease Scores of which higher scores indicated ease, were 23.86±9.38 and 44.54±14.66 ($p=0.002$). The mean reading times were 15.6±2.85 and 10.17±2.17 seconds for ChatGPT and The Specialist, respectively ($p=0.003$). The overall reach of the answers by ChatGPT and The Specialist was 56.87±11.67 and 81.67±12.80 ($p<0.001$).

Conclusion: Although, ChatGPT provided appropriate answers to all compiled strabismus questions, those were complex or very difficult to read for an average person. The readability scores indicated a college graduation degree would be required to understand the answers provided by ChatGPT. However, The Specialist gave similar information in a more readable form. Therefore, physicians and patients should consider the limitations of such similar platforms for ocular health-related questions.

Keywords: Artificial intelligence, ChatGPT, Readability, Strabismus, Strabismus surgery

1. INTRODUCTION

As the field of artificial intelligence (AI) advances, several AI-powered search platforms have been developed to serve in various sectors, including healthcare. Those platforms are proposed to potentially assist patients and their caregivers with medical conditions and treatment options [1-3]. One of the AI-powered search platforms, Chat Generative Pre-trained Transformer (ChatGPT), a language model-based bot developed and released in November 2022 by OpenAI, has already surpassed 100 million users by January 2023 [3,4].

ChatGPT-4 is the latest version of the bot with improved performance, released in March 2023 [4,5]. However, due to the subscription-based paid nature of the latest version, most people still prefer using the open-access ChatGPT-3.5, which is still comparably reliable [5]. Nevertheless, despite its impressive capabilities, there are concerns about the reliability, readability, and comprehensiveness of the specific responses of the chatbot to common questions asked by patients as well as caregivers in several health-related conditions [1-3].

Various treatment options are available to address strabismus management in children, including non-surgical approaches like patching and refractive error correction, as well as surgical options. It is shown that parental stress is an issue that should be considered when treating children with ophthalmological disorders. To lower stress and achieve an optimal treatment environment for the patient, patients/caregivers should be well-informed about their conditions. Nowadays, it is common

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knowledge that people seek detailed answers to their questions online, even after doctor visits. Therefore, health workers should be aware of the advantages/risks of online data [2].

Several studies have already investigated the accuracy and readability of health-related online data freely or by AI-based chatbots [1-3, 6-8].

However, to our knowledge, no previous studies are available regarding the appropriateness and readability of content provided by online AI-based systems on common questions asked by patients or caregivers on managing strabismus. Therefore, this study aims to evaluate the answers to the common questions about strabismus management provided by ChatGPT-3.5 and to compare them to the responses of a strabismus specialist in terms of appropriateness and readability.

2. MATERIALS and METHODS

This cross-sectional study was exempted from ethics committee approval by the Marmara University Institutional Review Board since it did not involve human subjects. This study was conducted using the open-access language model ChatGPT-3.5 [4] and the open-access online readability tool Readable [9] in August 2023.

The authors compiled a list of the 15 most common questions asked by the patients or their caregivers at Marmara University Pendik Training and Research Hospital, Istanbul, Turkey, outpatient Pediatric Ophthalmology and Strabismus Clinic about the surgical and non-surgical treatment options for strabismus, the prognosis of strabismus, postoperative care of the patients, and strabismus surgery-related complications. The compiled questions are listed in Table I.

Table I. *The compiled common questions asked by the patients or their caregivers in our outpatient pediatric ophthalmology and strabismus clinic.*

1.	Is there a possibility to correct strabismus with glasses or medication?
2.	What is the rate of success in strabismus surgery?
3.	Will the visual acuity improve with the strabismus surgery?
4.	Is there a risk of strabismus recurrence?
5.	Is there a risk of blindness after the strabismus surgery?
6.	Is there a risk of strabismus worsening after the surgery?
7.	Are we going to continue wearing glasses after the surgery?
8.	Will the lazy eye improve after the strabismus surgery?
9.	If recurrence occurs after the initial surgery, is there a chance for another surgery?
10.	Is it better to have the strabismus surgery after the age of eighteen?
11.	Is there a risk of double vision after the strabismus surgery?
12.	Is the strabismus surgery performed with lasers?
13.	How long will the patient stay in the hospital after the strabismus surgery?
14.	Will medication be required after the surgery?
15.	How frequently will follow-up appointments be scheduled after the surgery?

Appropriateness

One of the strabismus specialists (The Specialist; D.D.Y.) answered all compiled questions to provide accurate, evidence-based, and comprehensible responses intended to be understandable by the public audience. Those answers were set as the reference for appropriateness evaluation. The questions were asked two times on the ChatGPT-3.5 platform. For the second time, ChatGPT was asked to summarize the first answers into a shorter and more readable version, i.e., the final version. The final version of the answers to each question provided by ChatGPT were classified as "appropriate" or "inappropriate" according to the reference answers provided by The Specialist.

Readability

The readability of all answers ChatGPT and The Specialist provided was assessed using seven indices from the Readable online toolkit [9]. Those indices included the Flesch Reading Ease Score (FRES), Flesch-Kincaid Reading Grade Level (FKRGL) Scores, Gunning Fog Index, Coleman-Liau Index, Simple Measure of Gobbledygook (SMOG) Index, Reading Time (in seconds), and Overall Reach.

Flesch readability tests (FRES and FKRGL) use mathematical formulas based on the sentence length, word count, and number of syllables for each word [10,11]. The FRES ranges between 0 (unreadable) and 100 (very easy to read), with higher numbers indicating easier readability. The corresponding score ranges between very difficult (i.e., scientific papers), difficult (i.e., academic papers), fairly difficult, standard (i.e., easily understandable by 13 – to 15-year-olds), fairly easy, easy, and very easy (i.e., comics) to read texts are 0-30, 30-50, 50-60, 60-70, 70-80, 80-90, and 90-100 points, respectively [10,12]. The scores obtained from FKGRL approximately correspond to the United States grade levels (i.e., a text with a FKGRL score of 8.2 can be interpreted as understandable by an average person who graduated from 8th Grade) [11,12].

The Gunning Fog Index assesses the average length of sentences in combination with the rate of polysyllabic words. The index score ranges from 0 to 20 and measures clarity and simplicity. The Coleman-Liau index is usually used in addition to other indices and is especially useful in medical documents. It is based on sentence length and an average number of letters per 100 words. The SMOG index uses the frequency of polysyllabic words in a sample of sentences 13]. It is instrumental in health care and measures comprehensiveness. The results from the latter three indices correspond to the school grade level of a person to understand a piece of text, such as FKGRL. The lower the Gunning Fog index, Coleman-Liau index, and SMOG index scores are, the easier the text to read and comprehend.

Overall reach measures the proportion of the target audience that can read given content easily. It is currently calibrated against the literate general public, so a reach of 100% means your content is readable by about 85% of the public (the literate percentage).

Statistical Analysis

Descriptive statistics were given as mean, standard deviation, median, minimum, maximum, frequency, and ratio values where relevant. The distribution of data was analyzed with the Kolmogorov-Smirnov test. Independent sample t-test and Mann-Whitney U test were used to analyze quantitative independent data. Wilcoxon test was used in the analysis of dependent quantitative data. The chi-square test was used to analyze qualitative independent data, and the Fischer test was used when the chi-square test conditions were not met. The analysis was made using SPSS software for IOS, version 28.0 (SPSS Inc, Chicago, IL). The significance level was set as $p<0.05$.

3. RESULTS

The appropriateness evaluation showed 100% agreement between The ChatGPT and The Specialist.

The evaluated readability indices of The ChatGPT and The Specialists are given in Table II.

Table II. *The comparison of the answers provided by The Specialist and ChatGPT in terms of readability.*

Readability Indices	The Specialist Mean ± SD Median (Min-Max)	ChatGPT Mean ± SD Median (Min-Max)	P-value†
FRES	44.54 ± 14.66 43.96 (14-67)	23.86 ± 9.38 20 (12-39)	**0.002**
FKRGL	10.17 ± 2.17 10.36 (6-13)	13.75 ± 1.55 13.93 (11-15)	**<0.001**
Gunning Fog Index	13.32 ± 3.0 13.44 (8-17)	18.34 ± 2.74 18.21 (13-23)	**<0.001**
Coleman-Liau Index	12.19 ± 1.87 11.93 (8-15)	16.41 ± 1.64 16.57 (12-18)	**<0.001**
SMOG Index	12.70 ± 1.83 13.02 (8-15)	15.90 ± 1.74 15.65 (13-19)	**<0.001**
Reading Time‡‡	10.17 ± 2.17 9 (4-23)	15.6 ± 2.85 16 (10-20)	**0.003**
Overall Reach	81.67 ± 12.80 82 (59-100)	56.87 ± 11.67 56 (40-77)	**<0.001**

FKRGL: Flesch-Kincaid Reading Grade Level, FRES: Flesch Reading Ease Score, SD: Standard Deviation, SMOG: Simple Measure of Gobbledygook. † Wilcoxon Signed-Rank Test, ‡ Evaluated in seconds, Bold values indicate statistical significance.

The mean FKGL of the answers given by ChatGPT and The Specialist were for university sophomore and high school sophomore grade level audiences, respectively. The mean FRES results indicated reading the answers of The Specialist was nearly twice as easy as ChatGPT's. It is noted that the responses of ChatGPT were very difficult; meanwhile, the responses of The Specialist were merely difficult to read. All three Gunning Fog, Coleman-Liau, and SMOG indices scores indicated clearer and easier-to-understand responses by The Specialist, with significantly less reading time.

4. DISCUSSION

Recently, there has been an increasing interest in using AI-based systems. However, only a small portion of opportunities in clinical practices were discovered. There are a lot of advantages and pitfalls waiting to be evaluated while adapting our understanding of healthcare to the future [1,14].

In a study evaluating the performance of ChatGPT on various ophthalmology examinations, it was stated that the accuracy of the AI-based model was 59.4% and 49.2% [5]. They also noted that this outcome was noteworthy and promising in ophthalmology; as the questions get more specific on a subject, the accuracy falls [5,15]. In our study, we asked commonly asked questions by patients and caregivers and tried to have simple, not-too-detailed, and understandable responses. We observed that ChatGPT-3.5 was able to provide appropriate answers to those of a strabismus specialist regarding strabismus management.

We used five indices, as proposed by Momenaei et al., to evaluate the readability of every response given by ChatGPT-3.5 and the strabismus specialist [2]. The mean FRES for The Specialist was between 30 and 50, indicating an appropriate level for merely 33% of the population. However, the score of ChatGPT was even lower, between 0 and 30, meaning it was a very hard level of reading, which was readable for only 4.5% of the US population [2,16]. The FKRGL scores ranged from 0 to 30 for both ChatGPT and The Specialist, indicating that the responses were very hard to understand and that college graduation would be required to understand all the answers given.

The mean Gunning Fog Index of The Specialist was 13.32, meaning an average first-year college student could understand the answers. However, the mean Gunning Fog index of ChatGPT was 18.34, implying that the answers were readable for post-graduates [16,17]. Meanwhile, the mean Coleman Linau Index scores, showing the grade level in the US school system required to understand a text, were between 10-13 for The Specialist (12.19) and higher than 13 for ChatGPT (16.14). Those results indicated a reading ability necessitating a high school and college education for the answers of The Specialist and ChatGPT, respectively. Also, the mean SMOG Index results, showing year estimates of schooling needed to comprehend a text, were higher for the answers given by ChatGPT (12.70) than The Specialist (15.90). This index was stated as a measure of the readability of consumer-focused healthcare materials [6].

The Overall Reach score of ChatGPT was also lower than that of The Specialist, indicating that answers generated by ChatGPT-3.5 seem too complicated for the general population.

This study has some limitations, like the variability of the responses of AI-based systems as the training data and the version of the system change. The current database is based on internet data until September 2021, which limits its ability to give more recent data. The results found in this study also will not apply to the newer ChatGPT versions. There are other popular language models, and they could have been included in the comparison with ChatGPT. Also, the accuracy of the responses were not scored according to a scale, but only categorized as

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appropriate or inappropriate. On the other hand, the strengths of this study are the comparison of the publicly available version of the ChatGPT and the evaluation of readability by multiple indices.

In conclusion, this study showed that ChatGPT-3.5 might provide highly accurate answers to common questions about surgical and non-surgical treatment options for strabismus, prognosis, postoperative care, and surgery-related complications. However, clinicians should be aware of that the responses given by AI-based models to medical inquiries are still more challenging to read and understand than the responses of the medical specialists by the general audience.

Compliance with Ethical Standards

Ethical approval: This cross-sectional study was exempted from ethics committee approval by the Marmara University Institutional Review Board since it did not involve human subjects.

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Evaluation of sleep quality in patients with idiopathic intracranial hypertension

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ABSTRACT

Objective: Idiopathic intracranial hypertension (IIH) is a condition that has no known cause and progresses with increased cerebrospinal fluid (CSF) pressure. Sleep apnea or other sleep disorders may occur with increased intracranial pressure (ICP). This study aims to determine the relationship between the signs and symptoms of IIH and sleep quality.

Patients and Methods: Three self-reported questionnaires, namely The Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), and the Beck Depression Inventory (BDI)) were administered to 31 IIH patients and the same number of controls and the scores were compared. Scores were analyzed according to the presence of symptoms in the IIH group. The correlation of these scores with ICP was evaluated.

Results: Between the two groups, the IIH group had significantly higher PSQI scores (p=0.009). Also, a significant relationship was shown between papilledema and PSQI scores (p=0.017); patients with papilledema had lower PSQI scores than patients without papilledema. BMI values were higher in patients without papilledema (p = 0.031). In the IIH group, PSQI and BDI scores had a positive correlation (r = 0.638, p < 0.001).

Conclusion: Sleep quality is impaired in patients with IIH, and the effect of being overweight in this deterioration is more pronounced than presence of papilledema.

Keywords: Idiopathic intracranial hypertension, Sleep quality, cerebrospinal fluid pressure, Papilledema

1. INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a condition in which cerebrospinal fluid pressure (CSF) is found to be elevated by lumbar puncture (LP) without an underlying cause such as an intracranial mass lesion or cerebral venous sinus thrombosis that could explain the increased intracranial pressure (ICP) [1]. The pathogenesis is unknown, but it is thought to result from a defect in CSF absorption ultimately. Overweight women of reproductive age are more affected [2]. It may present with headache, visual impairment, and pulsatile tinnitus, but the symptomatology is variable, leading to diagnosis delay [3]. Headache is reported in 75-99% of patients and does not have specific characteristics. Although, it may be in the vertex or suboccipital region, it is usually holocranial and may increase with awakening and the Valsalva maneuver [2].

Idiopathic intracranial hypertension and sleep disorders are linked with other diseases, such as headache and obesity, and it is estimated that the relationship between these two conditions arises from circadian rhythm or neurotransmitter changes [4]. The relationship between sleep quality and IIH is primarily associated with obesity-related obstructive sleep apnea (OSA) in adults. In OSA, apnea cycles are thought to cause episodes of hypoxemia and hypercapnia, leading to cerebral vasodilation and fluctuations in arterial blood pressure. As a result, an increase in ICP may lead to the development of papilledema [5].

In this study, we aimed to evaluate the quality of sleep in IIH patients and to reveal the relationship between IIH symptoms.

2. PATIENTS and METHODS

Between April 2023 and January 2024, 31 patients over 18 who were followed up with the diagnosis of IIH at the neurology

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outpatient clinic at Bezmialem Foundation University Hospital were included in the study. All included patients had previously applied to the outpatient clinic with a complaint of headache and were diagnosed with IIH after brain magnetic resonance imaging (MRI) and lumbar puncture. When the data obtained from the patient files were examined, CSF opening pressures of all patients after their first admission were above 200 mm H2O, and no other organic brain pathology that could increase ICP was detected on MRI findings. IIH was diagnosed according to the modified Dandy criteria revised in 2014 [6]. Thirty-one healthy volunteers older than 18 with normal neurologic examination were included in the control group. The study was approved by the Bezmialem Foundation University Hospital Clinical Research Ethics Committee (Approval No: E-54022451-050.05.04-102723, Date: 03.04.2023). All participants were informed verbally, their written informed consent was obtained, and the Declaration of Helsinki was followed in all procedures.

In the IIH group, gender, age, body mass index (BMI) and medical history (including symptoms of headache, nausea, blurred vision, diplopia, dizziness, tinnitus, transient blurred vision, and papilledema), neurological and ophthalmological examination findings were recorded. The patients were administered the Pittsburgh Sleep Quality Index to assess sleep quality (PSQI) [7], the Epworth Sleepiness Scale to determine sleepiness (ESS) [8], and the Beck Depression Inventory (BDI) to assess depressive tendencies, and the scores were recorded. Cerebrospinal fluid opening pressure was obtained from the patient's previous files. Demographic data and PSQI, ESS, and BDI scores were recorded in the control group. BMI values above 25 kg/m2 were considered overweight [9].

Statistical Analysis

We used SPSS software version 26 (IBM, Armonk, NY, USA) for statistical analysis. Frequencies and percentages represented categorical variables. Mean and standard deviation represented continuous variables that follow a normal distribution. For non-normally distributed data, values were presented as medians with minimum and maximum values. Shapiro-Wilk test was performed to assess if data followed a normal distribution. For normal distributions, an independent-sample t-test was used to compare quantitative data. For non-normal distributions, a Mann-Whitney U test was employed. The statistical significance level was 0.05.

3. RESULTS

Twenty-nine women (93.5 %) and two men (6.5 %) were in the IIH group. There were 31 individuals, and the same proportion of women (93.5 %) and men were in the control group. The mean ages of the IIH and healthy controls were 39.90 ± 10.22 and 39.77 ± 10.26 years, respectively (p = 0.961). IIH and healthy controls had mean BMI values of 25.03 ± 1.91 kg/m2 and 23.11 ± 1.83 kg/m2, respectively (p = 0.000) (Table I). The most common symptom was a headache (96.8 %, n = 30). Other symptoms included tinnitus (16.1%, n = 5), transient visual obscuration (19.4%, n = 6), blurred vision (25.8%, n = 8), diplopia (6.5%, n = 2), dizziness (16.1%, n = 5), nausea (19.4%, n = 6). Bilateral papilledema was detected in 23 patients (74.2%). Fourteen of the IIH patients were overweight and 9 (64 %) of these patients had papilledema.

Table I. *Demographic characteristics of the IIH group and the control group.*

	IIH = 31	Controls = 31	P
Sex, n (%)			
Male	2 (6.5)	2 (6.5)	
Female	29 (93.5)	29 (93.5)	1,000[a]
Age, years (mean ± SD)	39.90 ± 10.22	39.77 ± 10.26	0,961[b]
BMI, kg/m^2 (mean ± SD)	25.03 ± 1.91	23.11 ± 1.83	**0.000**[b]

[a]Chi-Square test, [b]Independent-sample t-test, IIH: Idiopathic intracranial hypertension, SD: Standard deviation

When comparing the IIH group and healthy individuals, the PSQI total score was significantly higher in the IIH group (p = 0.009). ESS and BDI scores showed no significant difference (p > 0.05) (Table II).

Table II. *Comparison of PSQI, ESS, and BDI scores of IIH and control group*

	IIH = 31	Controls = 31	P[a]
PSQI, median (min-max)	8 (4-19)	6 (0-15)	**0.009***
ESS, median (min-max)	6 (0-18)	5 (0-18)	0.198
BDI, median (min-max)	15 (0-41)	11 (0-54)	0.133

[a]Mann-Whitney U test, PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale, BDI: Beck Depression Inventory, min: minimum, max: maximum

When PSQI, ESS, and BDI scores were compared according to the presence of symptoms, the IIH group had significantly higher PSQI scores in patients without papilledema (p=0.017). No significant relationship was observed between other symptoms and scale scores (p > 0.05). These scores could not be compared with the presence of a headache because only one person did not have a headache (Table III). When patients with papilledema were compared with patients without papilledema, age was significantly lower in patients with papilledema (p=0.039). It was observed that BMI values in patients without papilledema were significantly higher than in the group with papilledema (p=0.031) (Table IV).

In the IIH group, the mean CSF opening pressure was 335.4 ± 64.8 mm H2O (min-max: 240–470). There was no correlation between PSQI, ESS, and BDI scores and CSF opening pressures (Table V). When the relationship between scale scores was evaluated, a positive correlation was observed between PSQI scores and BDI scores in the IIH group (r = 0.638, p<0.001).

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Table III. *The relationship between the presence of symptoms and PSQI, ESS, and BDI scores.*

		PSQI		ESS		BDI	
		median (min-max)	P[a]	median (min-max)	P[a]	median (min-max)	P[a]
Papilledema	**No (n=8)**	14.5 (8-16)	**0.017***	5 (1-12)	0.277	20 (7-37)	0.240
	Yes (n=23)	8 (4-19)		6 (0-18)		14 (0-41)	
Tinnitus	**No (n=26)**	8 (4-18)	0.765	6 (0-18)	0.590	15 (0-37)	0.389
	Yes (n=5)	8 (4-19)		5 (3-8)		25 (1-41)	
Transient Visual Obstruction	**No (n=25)**	8 (4-19)	0.189	5 (0-14)	0.304	14 (0-41)	0.707
	Yes (n=6)	10 (8-18)		11.5 (1-18)		18.5 (0-28)	
Diplopia	**No (n=28)**	8 (4-19)	1.000	5 (0-18)	0.545	15 (0-41)	0.717
	Yes (n=2)	10 (4-16)		7 (6-8)		13 (0-25)	
Dizziness	**No (n=26)**	8 (4-19)	0.892	5.5 (0-18)	0.686	15 (0-41)	0.146
	Yes (n=5)	8 (7-14)		6 (4-14)		31 (7-37)	
Blurry vision	**No (n=23)**	8 (4-19)	0.616	5 (0-14)	0.167	14 (0-41)	0.821
	Yes (n=8)	9.5 (4-18)		7.5 (1-18)		18.5 (1-28)	
Nausea	**No (n=25)**	8 (4-19)	0.245	5 (0-18)	0.920	15 (0-41)	0.920
	Yes (n=6)	12.5 (4-16)		6 (2-16)		18.5 (0-37)	

[a]Mann-Whitney U test, PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale, BDI: Beck Depression Inventory, min: minimum, max: maximum

Table IV. *Demographic characteristics of the patients with papilledema.*

	Patients with Papilledema n= 23	Patients without Papilledema n= 8	P
Sex, n (%)			
Male	2 (6.5)	0 (0)	
Female	21 (91.3)	8 (100)	0.389[a]
Age, years (mean ± SD)	37.70 ± 10.02	46.25 ± 8.34	**0,039**[b]
BMI, kg/m^2 (mean ± SD)	23.89 ± 2.22	26.40± 2.10	**0.031**[b]

[a]Chi-Square test, [b]Independent-sample t-test, IIH: Idiopathic intracranial hypertension, SD: Standard deviation

Table V. *Correlation between CSF opening pressure (mm H_2O) and PSQI, ESS, and BDI scores in the IIH group.*

	Spearman correlation coefficient, rho	P
PSQI	0.048	0.799
ESS	0.151	0.417
BDI	-0.069	0.711

CSF: Cerebrospinal fluid, PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale, BDI: Beck Depression Inventory

4. DISCUSSION

The present study showed that sleep quality is impaired in IIH patients. The clinical characteristics and pathophysiological features of patients with IIH and patients with sleep disorders overlap significantly. Obesity is an important risk factor for both conditions [10]. Studies also have extensively demonstrated the association between headache and sleep disturbance [11]. The association of primary headache syndromes with sleep disorders has been attributed to neurotransmitter or circadian rhythm changes [12]. Headache is the most accompanying symptom of IIH [13]. Lateralized throbbing pain may be aggravated by posture changes such as lying down. Headache often occurs on awakening [14]. The evidence that ICP rises during sleep is well established and was first demonstrated polygraphically in l966 [15]. Elevated ICP during sleep is explained by alterations in blood or CSF volume. The increase in ICP during rapid eye movement (REM) sleep secondary to an increase in cerebral blood volume has been associated with decreased sympathetic tone. In addition, decreased alveolar ventilation during sleep may also cause an increase in ICP [16]. Alperin et al., observed decreased jugular venous drainage and increased interstitial fluid volume in the gray matter in obese patients with IIH [17]. In the present study, the mean BMI of the IIH group was above 25 kg/m2. Except for one patient, all other patients described headaches. It is thought that these two conditions contribute to the deterioration in sleep quality.

Kornbluh et al., compared sleep problems in sixty-two pediatric IIH patients with a control group using the Child Sleep Habits Questionnaire. Statistically significant differences were found in total sleep disturbance score (p =.035), sleep onset delay (p =.014), parasomnias (p =.013), and sleep-disordered breathing (p =.013). The study showed that pediatric IIH was associated with increased sleep disturbances [15]. In a study conducted by Latzer et al., the sleep disorders in 33 adolescents with IIH and controls were compared using the School Sleep Habits Survey (SSHS), the Pediatric Sleep Questionnaire (PSQ), and the depression scale. Sleep disturbances were significantly higher in the IIH group (SSHS, $p < 0.001$; PSQ, $p < 0.001$). Sleep-related breathing problems ($p = 0.006$), sleepiness during the daytime

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(p = 0.04), sleep/wake disruptions (p < 0.001), and depressive complaints (p < 0.001) were also significantly higher in the IIH group. Sleep disturbance has been observed to be common in the IIH group, regardless of weight and symptomatology [4]. Consistent with these results, we showed that PSQI scores were significantly higher in the IIH group. PSQI consists of components assessing sleep quality, duration, efficiency and latency, sleep disturbance, use of medication for sleep, and dysfunction during the daytime, and the total score indicates a global sleep quality/disorder score. Higher scores indicate a more marked deterioration in sleep quality [18].

Compliance with Ethical Standards

Ethical approval: The study was approved by the Bezmialem Foundation University Hospital Clinical Research Ethics Committee (Approval No: E-54022451-050.05.04-102723, Date: 03.04.2023). All participants were informed verbally, their written informed consent was obtained, and the Declaration of Helsinki was followed in all procedures.

Conflict of interest: The authors declare that there is no conflict of interest.

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Authors contibutions: AY, DK: Methodology and design, Data collection, AY: Data analysis, AY, DK: Literature search, AY DK: Writing, AY: Writing and editing. Both authors read and approved the manuscript.

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Evaluation of balance disorder and associated factors in patients with ankylosing spondylitis

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ABSTRACT

Objective: The aim of this study was to investigate balance disorder and the factors associated with it in patients with ankylosing spondylitis (AS).

Patients and Methods: The study included 75 patients diagnosed with AS and 75 healthy volunteers. Patients and controls were analysed for demographic characteristics, and AS patients were also investigated for disease activity indices and disease duration. Patient and control groups were compared using static and dynamic balance tests.

Results: The scores of AS patients were found to be worse than the control group (p=0.000) in terms of Static Double-Feet Balance Index (SDFBI), Static Single-Feet Balance Index (SSFBI), Dynamic Balance Index (DBI), Timed Up and Go test (TUGT), Berg Balance Scale (BBS), Functional Reach Test (FRT) and Hand to Ground Distance (HGD). Balance impairment was significantly higher in patients with kyphosis and advanced stage of sacroiliitis. Kyphosis angle, stage of sacroiliitis, Bath Ankylosing Spondylitis Metrology Index (BASMI), OWD (occiput-to-wall distance) scores, presence of contracture in hip or knee joint and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were correlated with poor balance when evaluated with balance evaluation scales for correlation.

Conclusions: Balance was impaired in AS patients. Appropriate treatment and rehabilitation protocols for spinal and peripheric joint stiffness may improve balance disorder in AS patients.

Keywords: Ankylosing spondylitis, Posture, Balance

1. INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease affecting the axial skeleton, leading to inflammation in spinal joints and adjacent structures and progressive bone fusion in vertebra [1]. The fusions in vertebrae cause spinal mobility limitations and difficulties in daily living activities [2]. The changes in the vertebral structure become more evident as the disease progresses, and the vertebrae can turn into rigid bone bundles from occiput to sacrum, and even rigid thoracolumbar kyphotic deformity may occur [3]. Kyphotic deformity may cause the body's center of gravity to shift forward, making it difficult to perform daily living activities such as interpersonal communication, driving, walking, and personal hygiene [4, 5]. The characteristic posture of AS includes ventral flexion of the head and neck, increased thoracic kyphosis, and tightness of the hip and knee flexors [6]. It was reported that postural disorder leads to the impairment of balance and increased risk of falling [5]. Khan et al., reported that patients with AS may injure themselves more easily after sudden position changes due to spinal stiffness that impairs the ability to maintain balance [1, 6]. Although, postural alterations are considered to affect balance, the studies investigating balance problems in patients with AS have controversial findings. The number of studies investigating balance problems in AS and relevant factors are limited. While, some studies report that postural alterations have no effects on the balance of AS patients [7-10], others claim balance is impaired, and falling risk is increased [11-15]. Impairment of balance was linked to kyphosis [11,12,16,17], limitations in spinal mobility, advanced postural alterations [11-15], loss of

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proprioception [9,12,13,18], and disease activity [15] in the studies.

Investigations of the effect of ankylosing spondylitis on balance can illuminate the possible mechanism of fall risk in patients and emphasize balance training as part of treatment. This study aimed to investigate the effects of postural alterations on balance using the clinical balance assessment tools and the static and dynamic balance index.

2. PATIENTS and METHODS

Seventy-five patients diagnosed with AS according to the modified New York Criteria, and 75 healthy volunteers were included in the study. The study was approved by the Selcuk University, Faculty of Medicine, Non-interventional Ethics Committee (date. 28.04.2025, approval number: 2015/148), and the study was conducted in accordance with the Declaration of Helsinki for human and animal rights. Patients with neurological and/or metabolic diseases that cause balance disorder, those with orthopedic disorders that affect balance and spinal mobility, and those with a history of chronic alcohol use and taking medication that can lead to balance disorder, pregnants, malign disorders and under 18 and over 60 years of age were excluded from the study. All participants were informed about the design and aim of the study, and a consent form was obtained from all participants before the study.

The demographic features of all participants, such as date of age, gender, weight, height, body mass index (BMI), marital status, education level, occupational status, family structure, monthly income level, and duration of AS for the patient group were determined. Joint and extra-articular involvement were also evaluated in the AS group. For the AS group, the pain level and disease activity were assessed with the visual analog scale (VAS) of 0-10 cm and BASDAI, respectively. BASDAI is an index used to determine disease activity and evaluate the parameters, such as fatigue, spinal pain, peripheral arthritis, enthesitis, and severity and duration of morning stiffness [19]. The presence of contracture of hip and knee joints was recorded. All participants were assessed in the afternoon to avoid the effects of morning stiffness. The patients were asked not to take non-steroid anti-inflammatory drugs or exercise within 24 hours before evaluation to prevent changing BASDAI, BASMI, and VAS scores. Occiput-to-wall distance (OWD), tragus-wall distance, modified Schober, lumbar lateral flexion, cervical rotation, chest expansion, kyphosis angle, and BASMI measurements were compared between groups and in the AS group. BASMI includes five clinical measurements that reflect axial mobility to evaluate spinal mobility [20]. The AS patients were also classified according to the presence/absence of kyphosis, stage of sacroiliitis, and BASDAI. A physical medicine and rehabilitation specialist did the physical examination and took the spinal measurements.

All participants were compared in terms of the Static Double-Feet Balance Index (SDFBI), Static Single-Feet Balance Index (SSFBI), DBI, dynamic fall risk (DFR), static fall risk (SFR), Berg Balance Scale (BBS), Timed Up and Go test (TUGT), Functional Reach Test (FRT), and SportKAT 4000® (LLC-Vista, California, USA) device scores.

Berg Balance Scale is composed of 56 points, and a score of 45 or more is accepted as a good balance. Higher scores in BBS indicate better balance [21,22]. It was seen that people who completed TUGT in less than 20 sec had higher scores in BBS and had a normal gait speed (0.5 m/sec), which is necessary for walking in the community. However, it was observed that those who had completed TUGT at 30 sec or more were more dependent on daily living activities, needed assisted devices for ambulation, and got lower scores in BBS [23,24]. The reliability and validity of the Turkish version of BBS were made by Sahin et al. [25].

For FRT, the patients were asked to lift the upper limbs so that the shoulders were at 90° flexion and reached the furthest distance that could be reached without stepping and touching the wall. The measurements were repeated three times for each patient, and an average score was recorded [26,27].

Both static and dynamic balance measurements were performed with a SportKAT 4000® device (LLC-Vista, California, USA). The SportKAT 4000® is a platform moveable up to 20° and supported by a small pivot at the center point. The fixation of the platform is achieved by changing the pressure of the round pneumatic mechanism between the lower part of the unit and the platform. The inclined sensor in front of the platform is connected to a computer, recording the deviation of the platform. Patients stand up and try to move the platform as desired with the motion of the center of body weight. While doing this, they can follow their movements on the computer monitor located at eye level. During the test, the distance between the center point and reference position is calculated for each recording. The reference position may be a fixed point or a moveable cursor. Therefore, a score balance index (BI) is calculated by summing up the measurements of these distances. BI measures the individual's ability to hold the platform close to the reference position. On the device, the static mode evaluates static balance by asking the patient to keep the X symbol (center of body weight) at the center of the screen. Dynamic mode evaluates dynamic balance by asking the patient to move the platform in a way that follows a cursor or a pattern on the screen. The interval between the lowest and highest scores ranges from 0 to 6000. Lower scores indicate better balance. The scores are indirect identifiers of balance. Scores of 750 or more on SDFBI and SSFBI and 2000 or more on DBI are associated with an increased risk of falling. In our study, all tests were performed for 30 seconds after sufficiently training all patients and when pneumatic ground pressure was 6 (psi). For SSFBI, the test was evaluated on the dominant foot [28].

The Cobb angle was used to calculate thoracic kyphosis. The angle at the intersections of vertical lines arising from each of the parallel lines drawn from the upper edge of T3 and the lower edge of T12 was calculated as the thoracic kyphosis angle, and the value over 40° was evaluated as kyphotic deformity [29]. Radiographic sacroiliitis was assessed according to the modified New York criteria and graded between 0-4 [27].

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 (IBM Corp, Armonk, NY, USA). The Kolmogorov-Smirnov test checked whether the numerical variables were appropriate for normal distribution. The parametric and non-parametric data of the patients were compared with the student's t-test and chi-square test, respectively. The Mann-Whitney U and Kruskal Wallis tests were used to analyze the inappropriate distributions of the data. In determining the correlations between variables, Pearson's correlation analysis was used when parametric conditions were provided; otherwise, Spearman's correlation analysis was applied. A p <0.05 was accepted as a statistical significance level.

3. RESULTS

The demographic features of the patient and control group were similar in terms of age, height, weight, BMI, and gender (p>0.05) (Table I). When the patient and control groups were compared regarding SDFBI, SSFBI, DBI, BBS, TUGT, and FRT, all tests showed significant differences in favor of balance disorder for AS patients (Table II). When AS patients were divided according to the presence of kyphosis, a significant difference was found in SDFBI, SSFBI, DBI, BBS, and TUGT scores in patients with kyphosis. There was no significant difference between FRT scores (Table III). When AS patients were classified into three groups according to the stage of sacroiliitis, significant differences were found in SDFBI, SSFBI, DBI, TUGT scores, and kyphosis angle. There was no difference in BBS and FRT scores (Table IV).

Table I. *Sociodemographic and clinical features of patient and control group (with mean±SD)*

	Patients with AS (n=75)	Controls (n=75)	P
Age (years)	36.56±10.32	33.71±8.16	.062
Height (cm)	168.63±8.85	170.96±9.19	.115
Weight (kg)	70.97±14.46	71.68±11.52	.741
BMI (kg/cm²)	24.90±4.40	24.54±3.69	.593
Gender			
Female	24 (32%)	25 (33.3%)	.862
Male	51 (68%)	50 (66.7%)	
Duration of disease (years)	7.71±6.83	-	
BASFI	3.50±2.73	-	
BASDAI	4.49±2.08	-	
BASMI	2.80±2.70	-	

AS: *Ankylosing Spondylitis,* ***BASMI:*** *Bath Ankylosing Spondylitis Metrology Index,* ***BASDAI:*** *Bath Ankylosing Spondylitis Disease Activity Index,* ***BASFI:*** *Bath Ankylosing Spondylitis Functional Index,* ***BMI:*** *Body mass index*

Correlation analysis revealed that kyphosis angle was moderately positively correlated with SDFBI (p<0.001, r=0.393), SSFBI (p=0.002,r= 0.345), DBI (p=0.008, r=0.304) and TUGT scores (p=0.001, r= 0.544) and moderate negatively with BBS (p=0.001, r=-0.522). Stage of sacroilitis was moderate positively correlated with SDFBI (p=0.001, r=0.387), SSFBI (p=0.001, r= 0.370), DBI (p=0.019, r=,0.270) and TUGT scores (p=0.00, r= 0.436) and weak negatively with BBS (p=0.025, r=-0.258). BASMI scores were moderate positively correlated with SDFBI (p=0.000, r=0.444), SSFBI (p=0.009, r= 0.301), DBI (p=0.009, r=,0.299) and TUGT scores (p=0.001, r= 0.732) and moderate negatively with BBS (rp=0.001, r=-0.692). OWD scores was moderate positively correlated with SDFBI (p=0.001, r=0.371), SSFBI (p=0.003, r= 0.341) and TUGT scores (p=0.000, r= 0.669), weak positively correlated with DBI (p=0.013, r=,0.286) and moderate negatively with BBS (p=0.001, r=-0.575). Presence of contracture was weak positively correlated with SDFBI (p=0.031, r=0.249), SSFBI (p=0.018, r= 0.273), moderate positively correlated with DBI (p=0.004, r=0.327) and TUGT scores(p=0.001, r=0.403) and moderate negatively with BBS (p=0.000, r=-0.486).

Also, there was a moderate positive correlation between BASDAI and SDFBI (p=0.001, r=0.363) and DBI (p=0.005, r=0.320) and a moderate negative correlation between BASDAI and BBS scores(p0.001, r=-427) (Table V).

Table II. *Balance test scores in ankylosing spondylitis patients and control group with mean±SD*

	Patients with Ankylosing Spondylitis (n=75)	Controls (n=75)	P
HGD	14.07±11.90	3.15±4.79	<0.000
FRT	25.53±8.07	32.2±4.26	<0.000
BBS	53.67±3.54	56±0.00	<0.000
TUGT	10.95±2.70	9.01±0.12	<0.000
SDFBI	359.47±95.90	218.23±44.75	<0.000
SSFBI	405.87±117.37	225.12±53.94	<0.000
DBI	2476.31±542.84	2615.00±305.43	<0.0010

SDFBI: *Static Double-Feet Balance Index,* ***SSFBI:*** *Static Single-Feet Balance Index,* ***DBI:*** *Dynamic Balance Index,* ***TUGT:*** *Timed Up and Go test,* ***BBS:*** *Berg Balance Scale,* ***FRT:*** *Functional Reach Test,* ***HGD:*** *Hand to Ground Distance*

Table III. *Balance scores in ankylosing patients with and without kyphosis with mean±SD*

	With Kyphosis (n=45)	Without Kyphosis (n=30)	P
SDFBI	387.22±96.57	317.83±79.54	0.003
SSFBI	445.29±114.96	346.73±95.26	0.001
DBI	2602.78±529.77	2286.60±513.85	0.007
TUGT	11.78±3.14	9.70±10.01	<0.0010
BBS	52.69±4.16	55.10±1.64	0.002
FRT	24.28±9.03	27.04±6.05	0.139
BASMI	3.71±3.00	1.43+1.33	0.001

SDFBI: *Static Double-Feet Balance Index,* ***SSFBI:*** *Static Single-Feet Balance Index,* ***DBI:*** *Dynamic Balance Index,* ***TUGT:*** *Timed Up and Go test,* ***BBS:*** *Berg Balance Scale,* ***FRT:*** *Functional Reach Test,* ***BASMI:*** *Bath Ankylosing Spondylitis Metrology Index*

Table IV. *Association between radiographic sacroiliitis stage and balance tests with mean±SD*

	Stage 2 (n=13)	Stage 3 (n=22)	Stage 4 (n=40)	p
SDFBI	311.31±59.22	319.23±75.66	397.25±100.68	0.001
SSFBI	343.85±69.47	369.40±118.26	446.07±115.91	0.004
DBI	2104.38±318.31	2527.59±607.87	2568.97±522.09	0.019
Angle of kyphosis	34.01±8.11	40.53±11.73	48.52±11.83	<0.001
BBS	55.23±1.42	54.45±2.02	52.70±4.39	0.088
TUGT	9.42±0.76	10.48±2.41	11.7±3.01	0.001
FRT	28.50±7.26	26.95±6.91	23.56±8.47	0.112
BASMI	0.83±1.11	1.68±1.32	4.05±2.99	<0.001

SDFBI: *Static Double-Feet Balance Index,* ***SSFBI:*** *Static Single-Feet Balance Index,* ***DBI:*** *Dynamic Balance Index,* ***TUGT:*** *Timed Up and Go Test,* ***BBS:*** *Berg Balance Scale,* ***FRT:*** *Functional Reach Test,* ***BASMI:*** *Bath Ankylosing Spondylitis Metrology Index*

Table V. *Correlation of measurement parameters with balance tests*

	SDFBI	SSFBI	DBI	TUGT	BBS
Angle of kyphosis					
r	.393**	.345**	.304**	.544**	-.522**
p	<0.001	.002	.008	<0.001	<0.001
Stage of sacroiliitis					
r	.394**	.364**	.278*	.326**	-.290*
p	.001	.001	.019	<0.001	.025
BASMI					
r	.444**	.301**	.299**	.732**	-.692**
p	<0.001	.009	.009	<0.001	<0.001
BASDAI					
r	.363**	.092	.320**	-.427**	.222
p	.001	.494	.005	<0.001	.055
OWD					
r	.371**	.341**	.286*	.669**	-.575**
p	.001	.003	0.013	<0.001	<0.001
Contracture in hip or knee joint	.249*	.273*	.327**	-.486**	.403**
r	.031	.018	.004	.000	.000
p					

**. Correlation is significant at the 0.01 level (2-tailed). *.Correlation is significant at the 0.05 level (2-tailed).

SDFBI: *Static Double-Feet Balance Index,* ***SSFBI:*** *Static Single-Feet Balance Index,* ***DBI:*** *Dynamic Balance Index,* ***TUGT:*** *Timed Up and Go Test,* ***BBS:*** *Berg Balance Scale,* ***FRT:*** *Functional Reach Test,* ***BASMI:*** *Bath Ankylosing Spondylitis Metrology Index* ***BASDAI:*** *Bath Ankylosing Spondylitis Disease Activity Index,* ***OWD****:Occiput-Wall Distance*

4. DISCUSSION

In this study, we searched balance disorders in patients with AS and compared the findings with the control group. Also, the association of balance with kyphosis and the stage of sacroiliitis was investigated. In the study, balance impairment was significantly higher in patients with kyphosis and those in the advanced stage of sacroiliitis. Kyphosis angle, stage of sacroiliitis, BASMI, OWD scores, contracture in hip or knee joint, and BASDAI were correlated with poor balance. In a recent study, Cinar et al., reported that balance was disrupted in AS patients compared to healthy individuals, and the severity of balance disorder was correlated with BASMI score [12]. He also emphasized that dynamic balance could be affected more in patients with advanced spinal limitations, and in another study conducted using the Biodex Balance System, reported that the falling risk index scores increased in AS patients compared to the controls [7]. We found that balance was impaired in AS patients compared to the healthy controls, therefore, our findings are consistent with those of these studies.

Durmus et al., found late-stage postural changes, especially in kyphosis, diminished postural stability and in balance in AS patients [10]. Similarly, Batur et al., reported that increased kyphosis causes balance disorder due to the failure of anteroposterior stabilization [13]. Our study showed that SDFBI, SSFBI, DBI, BBS, and TUGT scores significantly differed in AS patients with kyphosis, indicating worse balance scores. Gunduz et al., observed that AS patients who had advanced kyphosis and limitations of spinal mobility limitations had difficulty in providing static and dynamic balance [11]. These results suggest that kyphosis may have an important role on balance in AS patients. So, preventing spinal stiffness and kyphosis or treatments focusing on kyphosis may be beneficial for balance disorder in AS patients.

In the literature, we encountered no studies investigating the association between the stage of sacroiliitis and balance problems in AS patients. In our research, the stage of sacroiliitis was moderately correlated with SDFBI, SSFBI, DBI, and TUGT scores, and there was a negative correlation between the stage of sacroiliitis and BBS. These findings suggest that balance disorder may be associated with the stage of sacroiliitis.

In our study, there was a positive correlation between BASDAI and SDFBI or DBI scores and a negative correlation between BASDAI and BBS scores, suggesting that disease activity has undesirable effects on balance. This finding is consistent with the study of Vergara et al. [16]. Hence, control of disease activity with meticulous medical treatment could improve balance in AS patients and reduce falling risk.

Occiput-to-wall distance scores were positively correlated with SDFBI, SSFBI, DBI, and TUGT scores and negatively correlated with BBS. In a similar study, Batur et al., reported that OWD was associated with balance disorder [13]. As a sign of postural impairment, OWD may be an indicator of balance disorders in AS patients. The presence of contracture of the hip or knee joint was correlated with poor balance, as may be expected, but we did not meet data about contracture and balance relation in AS patients in the literature.

The most important limitation of our study is using clinical balance assessment tests developed for neurologic and geriatric patients. There is no balance assessment tool specific to AS. However, the sample size and different balance assessment tools may be considered powerful aspects of the study.

According to the literature, progression of spinal and peripheric joint involvement and disease activity were correlated with poor

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balance in AS patients. So, prevention of disease progression and control of disease activity play an important role in balance. Management of balance disorder is crucial for these patients. Appropriate treatment and rehabilitation protocols for spinal and peripheric joint stiffness may improve balance disorder and daily living activities by restoring mobility and preventing balance-associated injuries [18,30]. Further studies, including larger populations, are required. Also, developing specific balance assessment tools for AS will provide a more favorable evaluation of balance disorder.

Compliance with Ethical Standards

Ethics committee approval: The study was approved by the Selcuk University, Faculty of Medicine, Non-interventional Ethics Committee (date: 28.04.2015, approval number: 2015/148), and the study was conducted in accordance with the Declaration of Helsinki for human and animal rights. All participants were informed about the design and aim of the study, and a consent form was obtained from all participants before the study.

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Authors contributions: AAI: Conception, design, materials, literature review, writer, data collection, analysis/interpretation, HY: Design, crtical review, literature review, analysis/interpretation, supervision, HG: Literature review, writer, critical review, supervision. All authors approved the final version of the article.

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The relationship between sacroiliac joint MRI scores and central sensitization in axial spondyloarthritis: A cross-sectional study

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ABSTRACT

Objective: To investigate the relationship between sacroiliac joint (SIJ) involvement and central sensitization (CS) in patients with axial spondyloarthritis (axSpA).

Patients and Methods: Twenty-four patients with axSpA were included in this study. CS was investigated via pressure pain threshold (PPT), temporal summation (TS), conditional pain modulation (CPM), and the central sensitization inventory (CSI). Sacroiliac joint involvement was assessed using the magnetic resonance imaging (MRI)-based Canadian Spondyloarthritis Research Consortium (SPARCC) scoring system. CS-related parameters and SPARCC score correlations were analyzed.

Results: The median (IQR) sacroiliac PPT score for the right SIJ was calculated as 17.47 (4.43) and 17.67 (4.57) for the left SIJ. In the TS measurement, the right SIJ TS median (IQR) value was calculated as 4.0 (3.5) and 4.0 (2.75) for the left side. The median (IQR) value was 149.67 (107.5) for CPM and 45.0 (27.75) for CSI. The median (IQR) sacroiliac inflammation score was calculated as 3.0 (8.75), and the median (IQR) structural score was calculated as 7.0 (11.5). No correlation was found between SPARCC scores and PPT, TS, CPM, and CSI values.

Conclusion: In axSpA patients, there was no association observed between pain sensitivity measures and sacroiliac involvement. Further comprehensive studies are required, taking into account the complex nature of CS.

Keywords: Axial spondyloarthritis, Central sensitization, Quantitative sensory testing, Central sensitization inventory, SPARCC.

1. INTRODUCTION

Pain is the main symptom that shapes the treatment in axial spondyloarthritis (axSpA) patients, as in most musculoskeletal diseases. As per classical knowledge, chronic inflammatory low back pain is the typical presentation of the disease and when supported by imaging, the patient is diagnosed with axSpA [1]. In addition to being diagnostic, imaging determines the subgroup of the disease and the severity of the involvement, and can be used to evaluate the treatment response. The use of magnetic resonance imaging (MRI) for this purpose has now been established, and the spondyloarthritis (SpA)-related lesions have been described in detail by the Assessment of Spondyloarthritis International Society (ASAS). The presence of bone marrow edema (BME)/osteitis is essential for the definition of active sacroiliitis, and SpA related lesions are grouped under two main headings: sacroiliac joint (SIJ) lesions showing disease activity or structural damage [2]. These lesions are directly related to the patient's symptoms, and it has been reported that the presence of BME is significantly associated with night pain and morning stiffness in SpA [3]. Among the structural lesions, SIJ fat metaplasia was associated with insidious onset and SIJ sclerosis with night pain [4]. It has also been shown that disease activation parameters, particularly the Ankylosing Spondylitis Disease Activity Score (ASDAS), are longitudinally related to SIJ inflammatory lesions in male axSpA patients [5]. Although, inflammation and associated lesions are accepted as the main source of pain in these patients, current data reveal that more complex mechanisms play a role in the pain process in SpA than we thought. Here, peripheral and central sensitization occur as a result of the complex interaction between the immune system and the nervous system [6]. The process, which is defined as peripheral sensitization and starts with increasing responsiveness of nociceptors via inflammatory mediators, turns into central sensitization (CS) by affecting the central nervous system with the continuation of these maladaptive changes [7]. Quantitative

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Sensory Testing (QST) is the most commonly used method in the diagnosis of CS, and thermal, pressure, and mechanical pain threshold, temporal summation (TS), and conditional pain modulation are frequently preferred for this purpose. In recent years, the Central Sensitization Inventory (CSI) has been used as an alternative to QST in the investigation of CS due to its more practical and low cost. The prevalence of CS detected by CSI in axSpA patients was reported as 45%, and a strong correlation was found between CS and disease activation parameters Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and ASDAS-CRP [8]. Although, the CS-disease activation relationship has been demonstrated by frequently used clinical instruments, these evaluations based on the patient's complaints should be supported by more objective methods. It is important to understand this link because increased inflammatory burden in the axSpA may trigger pain sensitization or CS may mimic disease activation by increasing pain sensitivity. The correlation of SIJ MRI findings, which are also associated with the pain patterns of the patients and accepted as a semi-objective finding of inflammation, with CS may be a guide in understanding this connection. The Canadian Spondyloarthritis Research Consortium (SPARCC) scoring system is based on the scoring of SIJ lesions in these patients, allowing for easier assessment of disease involvement [9]. With this index, sacroiliitis activation and structural damage are scored as two discrete points according to the severity and extent of the lesions. In this study, it was aimed at investigating the relationship between SIJ involvement, which was evaluated by the SPARCC score, and CS in axSpA.

2. PATIENTS and METHODS

Design and Study Population

The study was performed cross-sectionally with 24 axSpA patients. The patients aged 18-75 years diagnosed with axSpA were recruited from a rheumatology outpatient clinic of a training hospital. Patients with sacroiliac MRI images taken within the last three months were included in this study. The exclusion criteria were the presence of other systemic inflammatory rheumatic diseases, peripheral vascular diseases, peripheral neuropathy, and spine diseases (e.g., symptomatic herniated disc, spinal stenosis), using centrally acting pain medications (e.g., pregabalin, duloxetine, opioids), or glucocorticoids (>10 mg prednisone or its equivalent) [10]. This study was approved by the Marmara University, School of Medicine Clinical Research Ethics Commmittee (date:08.01.2021, approval number: 09.2021.64) and written informed consent was obtained from all patients. In addition, the study has been registered on ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT05021783).

Clinical Variables

Demographic variables including age, gender, body mass index (BMI), and clinical variables including subtype of axSpA (radiographic-axSpA/non-radiographic-axSpA), duration of disease, diagnosis time, duration of morning stiffness (min), and plasma levels of C-reactive protein (CRP) were obtained. As disease activity measures, global pain scores on a 0-10 visual analog scale (VAS) and BASDAI were performed.

Pain Centralization Assessment

Central Sensitization Inventory (CSI)

The CSI is used to detect CS in a patient with chronic pain and consists of two parts, A and B. The part A consists of 25 questions about CS-related symptoms, and a score of 40 and above indicates the presence of CS. It is also accepted that the severity of CS increases with higher scores [11]. In part B, CS-related diseases are questioned, and only part A of the scale was used in this study. This scale has been demonstrated to be a reliable and valid tool in the Turkish population with chronic pain (test-retest reliability = 0.92, Cronbach's alpha = 0.93) [12].

Quantitative Sensory Testing (QST)

Pressure Pain Threshold

Sacroiliac PPT measurements were applied bilaterally at four points by a trained assessor (FNY) using a manual pain pressure algometer; the first point was located 1 cm medially and caudally from the spina iliaca posterior superior (SIPS) and 3 more laterally, medially, and cranially. The reliability of the measured points varied between ICC 0.60 and 0.82 [13]. A demonstration was performed on the left forearm volar side to ensure that patients understood the steps correctly before the test. On the patient lying in the prone position, a 1 cm2 algometer probe was placed vertically at each selected point, pressure was applied in a 1 kg/sec increment, and the probe was supported manually by the assessor at the bone surfaces to avoid translocation. The application was terminated once the patient reported pain, and this value was recorded as a PPT. The left trapezius muscle was used to evaluate the distant control point [14]. The PPT value of each point was calculated by averaging two applications 30 seconds apart. Low PPT scores were considered signs of peripheral sensitization, while low PPT values in the distant point were interpreted in favor of CS [15].

Temporal Summation

Temporal summation was evaluated over the trapezius muscle and sacroiliac joint with a manual algometer. It has been shown that TS can be detected with a manual algometer, and this method has acceptable reliability (test-retest ICC ranges of 0.77 and 0.94) [16]. For the measurement of sacroiliac joint TS, the point located 1 cm medial and caudally from the SIPS was preferred, and as with PPT, the left trapezius muscle was used to evaluate the distant control point. High TS scores were associated with pain sensitization.

Conditioned Pain Modulation (CPM)

In the CPM test, dysfunction of descending inhibitory pathways was investigated through the effect of the conditioned stimulus on the test stimulus [17]. A test stimulus was applied to the trapezius with pressure-inducing 4-point pain intensity on VAS. Then, as a conditioned stimulus, the patients were asked to

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keep their right hand in water at 7 C for 20 seconds. After the conditioned stimulus, the patients were asked to rate their pain by applying a retest stimulus at the same intensity as the first stimulus to the trapezius. In patients who could not keep their hands in water for 20 seconds, the retest stimulus was applied immediately after the patients took their hands out of the water. The ratio between the first and second VAS values multiplied by 100 was defined as the CPM score, and higher scores indicated better descending pain inhibition [18].

Sacroiliac MRI Scoring

The Spondyloarthritis Research Consortium of Canada (SPARCC) method was used in the sacroiliac magnetic resonance imaging (MRI) evaluation of the patients. In the assessment of sacroiliac joint (SIJ) inflammation, a signal increase consistent with bone marrow edema was scored in the T2-weighted STIR sequences, and the ICC for this method had been reported as 0.90-0.98 [9]. According to this system, in semicoronal 1.5 Tesla sacroiliac MRI sections, the SIJ was divided into sacral and iliac four quadrants. By examining six consecutive coronal slices, the increase in signal was scored as 0=normal signal and 1=increased signal. Therefore, the maximum total score for two SIJ in one section was 8, while an additional one point per joint is added for sections with intense signal increase and continuous signal increase located 1 cm or more from the articular surface. In this scoring, the maximum score in a single coronal section was 12, and the total was 72.

In the SIJ structural score, five consecutive coronal sections were examined in the T1 sequence, which included the cartilaginous part of the sacroiliac joint. The section where the cartilaginous part of the joint was first seen, which is called the transitional section, was determined, and it was investigated whether there were fat metaplasia, erosion, backfill, and ankylosis in the four quadrants of the SIJ. Of these, fat metaplasia and erosion were investigated in four quadrants, in the iliac and sacral sides, in a total of 8 regions, while backfill and ankylosis were evaluated in a total of 4 regions in the upper and lower half of the joint. In this way, fat metaplasia and erosion were scored between 0 and 40, and backfill and ankylosis were scored between 0 and 20 in five consecutive slices. All assessments were performed by two experienced rheumatologists who were trained in sacroiliac MRI reporting and completed the calibration modules developed for the SPARCC scoring system.

Statistical Analysis

Nonparametric tests were used in all analyses since the data did not show a normal distribution according to normality tests. Continuous data are presented as median and interquartile range (IQR) in accordance with a non-parametric distribution. The relationship between sacroiliac PPT, TS, CPM, CSI, and SPARCC scores was investigated by Spearman rank correlation. The Intraclass correlation coefficient (ICC) analysis was used to assess inter-rater reliability in SPARCC scoring. $P < 0.05$ was considered statistically significant, and all data were analyzed using SPSS version 20.0 (IBM Corporation, Armonk, NY, USA).

3. RESULTS

Twenty-four axSpA patients were included in this study. The median (IQR) age was 41.0 (15) in patients, and the rate of female patients was 67%. A comparison of patient characteristics according to CS is summarized in Table I.

Table I. *Comparison of patient characteristics according to CS*

	AxSpA patients (n:24)		
	CS positive (n: 14)	*CS negative (n: 10)*	*Diff. Sig. between CS+ and CS- P-value*
Age, years	42.5 (13.75)	38.5 (18.25)	0.472
Female (%)	11 (45.8)	5 (20.8)	0.204
BMI (kg/m^2)	26.55 (5.46)	28.24 (11.94)	0.841
R-AxSpA (%)	41.7 (10)	25.0 (6)	0.439
Disease duration, years	5.0 (7.69)	3.5 (9.0)	0.508
Morning stiffness (min.)	30.0 (120.0)	30.0 (67.75)	0.752
VAS pain (0-10)	7.5 (2.0)	6.5 (3.25)	0.437
CRP (mg/L)	3.0 (5.13)	4.5 (10.4)	0.585
BASDAI	5.75 (3.48)	5.15 (2.3)	0.709

Data are presented as median (IQR) or n (%), SD: Standard Deviation, BMI: Body mass index, VAS: visual analogue scale, CRP: C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

The median (IQR) sacroiliac PPT score, which is the sum of the PPT values of four points for the right SIJ, was calculated as 17.47 (4.43) and 17.67 (4.57) for the left SIJ. The median (IQR) PPT value of the trapezius, which is the distant point, was 3.60 (1.75). In the TS measurement, the right SIJ TS value was calculated as 4.0 (3.30) and 4.0 (2.75) for the left side. The median (IQR) value was 149.67 (107.5) for CPM and 45.0 (27.75) for CSI. All QST data are shown in Table II.

Table II. *QST and CSI values of the patients*

	Median (IQR)
Sacroiliac-R PPT	17.47 (4.43)
Sacroiliac-L PPT	17.67 (4.57)
Trapezius PPT	3.6 (1.75)
Sacroiliac-R TS	4.0 (3.5)
Sacroiliac-L TS	4.0 (2.75)
Trapezius TS	4.0 (3.0)
CPM	149.67 (107.5)
CSI	45.0 (27.75)

CSI: Central Sensitization Inventory PPT: pressure pain threshold, TS: temporal summation, CPM: conditioned pain modulation, CI: Confidence interval; R: right; L: left,

In the scoring of two different observers, the median (IQR) sacroiliac inflammation score was calculated as 3.0 (8.75), while the median (IQR) structural score was calculated as 7.0 (11.50). All values, including the sub-components of the structural score, are shown in Table III. The ICC was found to be 0.75 (CI:

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0.50-0.88) for the structural score, and 0.75 (CI: 0.51-0.89) for the sacroiliac inflammation score and these values indicates good reliability (p<0.001) (Table IV).

Table III. *Median values of SPARCC scores*

	Median (IQR)
SPARCC	
Structural score (total)	7.0 (11.5)
Fat metaplasia	6.75 (11.63)
Erosion	5.75 (6.0)
Backfill	0 (0.75)
Ankylosis	0 (0)
Inflammation score	3.0 (8.75)
Total SPARCC score	4.0 (9.25)

SPARCC: Spondyloarthritis Research Consortium of Canada

Table IV. *Inter-rater reliability of SPARCC structural and sacroiliitis scores*

	ICC (95% CI)	*P value*
SPARCC		
Structural score (total)	0.75 (0.50-0.88)	<0.001*
Fat metaplasia	0.87 (0.73-0.94)	<0.001*
Erosion	0.04 (-0.36-0.42)	0.435
Backfill	-0.04 (-0.43-0.36)	0.569
Ankylosis	0.98 (0.96-0.99)	<0.001*
Inflammation score	0.75 (0.51-0.89)	<0.001*

SPARCC: Spondyloarthritis Research Consortium of Canada;ICC: Interclass Coefficient; CI: Confidence interval

There was no significant correlation between sacroiliac PPT, TS, CPM, and CSI and SPARCC scores. The r values calculated in the correlation analysis of the structural score with the right and left sacroiliac joint PPT values were 0.046 and 0.044, respectively; for the sacroiliac inflammation score they were 0.054 and 0.063 (p>0.05). All correlation coefficients are shown in Table V.

Table V. *Correlations between SPARCC scores, QST and CSI*

	PPT		*TS*		*CPM*	*CSI*
	R-SIJ	L-SIJ	R-SIJ	L-SIJ		
SPARCC						
Structural score, r(p)	0.046 (0.832)	0.044 (0.837)	0.018 (0.935)	0.023 (0.914)	-0.126 (0.557)	0.133 (0.534)
Inflammation score, r(p)	0.054 (0.803)	0.063 (0.770)	0.081 (0.708)	-0.094 (0.662)	0.138 (0.519)	-0.068 (0.751)
Total score r(p)	0.123 (0.567)	0.022 (0.920)	0.097 (0.653)	0.053 (0.806)	0.021 (0.923)	-0.004 (0.986)

SPARCC: Spondyloarthritis Research Consortium of Canada, PPT: pressure pain threshold, TS: temporal summation, CPM: conditioned pain modulation, CSI: Central Sensitization Inventory, R: right; L: left, SIJ: Sacroiliac joint

When the patients were classified according to the presence of CS and their SPARCC scores were compared, no significant difference was found between the groups (Table VI).

Table VI. *Comparison of SPARCC scores according to CS*

	AxSpA patients (n:24)		
	CS positive (n: 14)	*CS negative (n: 10)*	*Diff. Sig. between CS+ and CS- P-value*
Structural score	10.75 (15.0)	12.0 (12.13)	0.709
Inflammation score	3.0 (6.5)	3.0 (16.25)	0.931
Total SPARCC score	34.83 (8.84)	36.08 (11.86)	0.886

Data are presented as median (IQR), CS: Central Sensitization; SPARCC: Spondyloarthritis Research Consortium of Canada

4. DISCUSSION

Taking into consideration the effect of CS on the clinical appearance of axSpA, this study investigated the relationship between inflammatory changes in the SIJ and quantitative parameters of pain sensitization.

We conclude that there was no association observed between pain sensitivity measures and sacroiliac involvement in axSpA patients. Subchondral bone marrow edema (BME) in the SIJ is the main pathological change responsible for disease activation and pain in SpA, as indicated by the ASAS MRI working group [19]. In cases where the pattern of osteitis is not evident, other active inflammatory lesions such as enthesitis, synovitis, and capsulitis are supportive. Radiologically, structural lesions such as sclerosis, erosion, fat infiltration, and new bone formation, in addition to active inflammatory lesions should also be assessed in patients with axSpA [20]. These inflammation-related lesions were gathered under two headings with SPARCC scoring, and their relationship with QST results was investigated; no significant correlation was found between QST, CSI, and SPARCC scores in axSpA patients. Although, there is a large body of research on the relationship between radiological findings and measures of pain sensitization in osteoarthritis (OA), there is a lack of available data on this topic in rheumatological diseases. Different studies have reported that the presence of synovitis and effusion on MRI is correlated with QST results in OA patients experiencing severe pain, but the identical connection with bone marrow lesions (BMLs) has not been shown [21, 22]. It has been reported that synovitis and effusion, among these OA-related lesions, are inflammatory in nature, while BMLs are mechanical lesions that occur as a result of microtrauma [23]. Similarly, in patients with hand osteoarthritis, local PPT values were found to be associated with radiographic findings of structural damage and the degree of synovitis detected on ultrasonography. Nevertheless, in this patient population, there was no correlation established between TS and radiological joint findings [24]. Considering the links between inflammation and pain sensitization in degenerative diseases like OA, it seems plausible that axSpA will exhibit a similar relationship. However, the heterogeneity of the radiological and QST methods used in the studies and the fact that the inflammation burden in spondyloarthritis is higher than in osteoarthritis, make it difficult to directly translate these results to axSpA patients.

The main mechanism in this regard is that inflammation-induced structural changes lead to an increase in nociceptor sensitization, first peripherally and then centrally [24].

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Accordingly, a causal and linear relationship can be expected between PPT and TS and the presence of inflammatory lesions in our patients, as in OA. Another theory is that, rather than being directly related to an increase in nociceptive input, CS in these patients may be brought on by circulating substances like cytokines [25]. It will be more challenging to demonstrate a direct correlation between QST and SIJ lesions in cases of CS that arise from systemic inflammatory mediators rather than from regional nociceptor sensitization. Considering that the main feature that distinguishes axSpA from OA is systemic inflammation, it is possible that a similar difference affects the pain sensitization process. In any case, CS can occur in axSpA in both ways, and the predominant mechanism and QST results may vary depending on the characteristics of local and systemic inflammation.

The process of assessing the endogenous analgesic mechanisms that contribute to the development of CS is known as conditioned pain modulation, or CPM. Apart from decreased CPM function, patients with CS are reported to have higher pain and increased BASDAI scores as compared to axSpA patients without CS [8]. Similarly, less effective CPM in patients with high disease activity at baseline has been demonstrated to be a major predictor of high disease activity continuing despite therapy in rheumatoid arthritis [26]. On the other hand, in a study examining the relationship between CPM and chronic rheumatic pain, it was found that although, CPM impairment was associated with pain severity, it was not associated with disease activity or other clinical parameters [27]. While there is compelling evidence connecting CPM to pain in different chronic musculoskeletal disorders, the findings in rheumatism appear to be inconsistent. In contrast to PPT and TS, which are regarded as clinical signs of pain sensitization, CPM represents the effectiveness of the endogenous analgesic system. Therefore, determining the effect of inflammatory lesions on this circuit will be more challenging than demonstrating its relationship with pain.

In similar studies, the effect of the simultaneous presence of acute and chronic lesions on pain sensitization and related parameters is unknown. As mentioned above, although, acute lesions seem to be more important in terms of activation of nociceptive pathways and circulating cytokines in the development of CS, structural lesions are also likely to affect the sensitization process in the subacute or chronic period. In this context, one of the possible reasons for this discrepancy between SPARCC scores and QST is the simultaneous presence of various inflammatory and structural lesions in many patients. Nencini et al., emphasized that the nociceptor mechanical response in an animal model changes with age and chronicity; this means that pain sensitization parameters may differ in the course of the disease depending on the structural changes [28]. In addition, it is accepted that disease activity and systemic inflammatory burden in the chronic period are relatively reduced in most patients under treatment. An association between SPARCC scores and QST results may have been obscured by the simultaneous presence of acute and chronic lesions in a significant portion of the participants in the study.

When interpreting all these results, it is useful to remember the complex nature of pain sensitization. Whether local or systemic, the sensitization process brought on by inflammation-mediated nociception takes on a unique clinical appearance when biopsychosocial variables are involved. The fact that not every patient with rheumatism develops sensitization indicates the restricted effect of inflammation in CS and the importance of defined individual characteristics such as gender, pain behavior, and self-efficacy. This multifactorial structure of the CS makes it difficult to reveal the role of specific components in this system, especially with limited patients.

The limitations of the study are the small number of patients, the lack of evaluation of spinal QST, and the inability to calculate the interobserver and intraobserver consistency for the QST because it was performed by a single practitioner. The inability to perform patient assessment and sacroiliac imaging simultaneously can be considered another limitation of this study.

The study's strengths include being the first to investigate the connection between CS and SIJ involvement in spondyloarthritis and its comprehensive assessment of pain sensitization, which takes into account PPT, TS, CPM, and CSI.

Conclusion

Whether rheumatic or not, inflammation is recognized to play a role in the process of pain sensitization. This relationship becomes even more significant in chronic pain on the basis of systemic inflammation. As the sacroiliac joint is the main site of involvement in patients with axSpA, it can be thought of as the primary focus where pain sensitization develops. This study did not show an association between QST and SPARCC scores, but the extent to which CS is influenced by underlying disease or biopsychosocial factors remains unclear. Comprehensive studies are required to examine how these elements interact with CS settings and one another.

Compliance with Ethical Standards

Ethical approval: This study was approved by the Marmara University, School of Medicine Clinical Research Ethics Commmittee (date:08.01.2021, approval number: 09.2021.64) and written informed consent was obtained from all patients. In addition, the study has been registered on ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT05021783). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Protective effects of saffron, safranal and crocin administration on vitamins (A, D, E, K) and protein carbonyl levels against CCI4-induced oxidative damage in rats

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ABSTRACT

Objective: The possible effects of saffron and its active components on oxidative stress are known. Protein carbonyls (PCO), formed due to protein exposure to oxidizing agents, are a newly researched topic. In this study, it was aimed to determine, antioxidant fat-soluble vitamins (A, D, E, K) and PCO values after saffron, safranal and crocin administration with carbon tetrachloride (CCl4) in rats.

Materials and Methods: Fifty-four Wistar albino male rats were randomly selected, and 9 groups of n=6 were formed. Vitamin levels in rat serum were determined by HPLC and PCO levels were determined by spectrophotometric method.

Results: A significant difference ($p<0.01$) was found between the CCl4 and the saffron, safranal and crocin groups. A significant decrease was observed in retinol and cholecalciferol values between CCl4 and saffron group ($p<0.05$, $p<0.001$), and a significant decrease in cholecalciferol and phylloquinone levels between CCl4 and safranal groups ($p<0.01$, $p<0.05$). Moreover, a decrease in cholecalciferol level ($p<0.05$) was determined between the olive oil, saffron and CCl4+crocin groups.

Conclusion: As a result, saffron and safranal have a protective effect against CCl4-induced oxidative damage to PCO, retinol, phylloquinone and cholecalciferol, and this effect may be due to the potent antioxidative effects of saffron and safranal.

Keywords: Carbon tetrachloride, Protein carbonyl, Saffron, Safranal, Vitamin

1. INTRODUCTION

Carbon tetrachloride (CCl_4) is a chemical that causes tissue damage by producing free radicals [1]. Cytochrome P450 metabolises CCl4-induced damage. Free radicals formed due to this metabolism cause oxidative stress on DNA, proteins, lipids and generally other components of the cell [2, 4]. Oxidative stress is a condition that manifests itself when certain chemicals or drugs are taken or when the antioxidant level in the organism decreases. CCl_4 is widely used as a model for screening the effects of drugs or plant extracts [5, 6]. Unraveling the mechanism of cellular metabolism is one of the topics that scientists have been researching for a long time [7]. This is because everything a living organism does occurs at the cellular level. Oxygen-breathing organisms are exposed to various reactive oxygen species (ROS) throughout their lives, which can directly or indirectly damage molecules such as DNA, lipids, and proteins [8]. ROS cause oxidative stress, which triggers the survival button in the cell by undergoing a series of reactions. Following this process, a balance was established with free radicals and various enzymatic or non-enzymatic structures in living cells, and various comments were made on the direction of this balance, which is still being made.

Protein carbonyls are elevated under various oxidative stress conditions. Amino acids, which are the main mechanisms of proteins, may undergo some deterioration in their structure under various oxidative stress conditions. These modifications, called carbonyl formation, may be an early sign of protein oxidation [9]. Oxidative damage occurs in proteins with reactive oxygen species (ROS) formed by a series of reactions by metal-ion catalyzed reactions (MCO), photochemical processes, ionizing radiation and enzyme-catalyzed redox reactions, accompanied

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by increased protein carbonyl levels [10, 11]. Due to the vital functions of proteins at the cellular level, their structures are damaged over time. It is essential to strictly control this damage and to maintain order [12].

Vitamins are organic compounds required in trace amounts for the body's basic functions. They are catalysts for reactions involving energy metabolism. Various studies have defined the main functions of fat-soluble vitamins (retinol, cholecalciferol, α-tocopherol, phylloquinone) in the organism, such as antioxidants, bone health, immune system, blood clotting and vision [13-16]. Plants make important contribution to the protection of our health. The main reason for this is the active substances in the content of the plants. Naturally found in various plants, these active substances have been defined as free radical inhibitors, oxygen scavengers or reducing agents [17].

Saffron (*Crocus sativus L.*) is a perennial, sedentary plant of the Iridaceae family. Saffron is mainly used to impart color, flavor and aroma to foods, and certain chemical components have been identified. Due to the unique properties of saffron and its components, it has attracted the attention of many researchers. The part of the saffron plant responsible for its color is crocin, while safranal and picrocrocrocin are responsible for its bitter taste and aroma [18]. Saffron is used both in folk and modern medicine for therapeutic purposes [19]. Numerous studies have revealed that saffron has cytotoxic, anticarcinogenic and antitumor properties [20].

Fat-soluble vitamins (A, D, E, K) work most safely and effectively in the context of nutrition when they are taken into living cells in appropriate doses through a rich diet. In addition, there are many studies in the literature that state that protein carbonyls are associated with excessive production of ROS species. From this perspective, this study focused on PCO and vitamins between the groups as a result of treatment with saffron and its active ingredients, safranal and crocin, by creating oxidative stress in rats due to CCl_4 application. In summary, this study aims to investigate the effects of CCl_4-triggered oxidative stress on vitamins and protein carbonyl levels in the serum of rats and whether saffron and its active components modulate these effects. In addition, this study will be important in contributing to the literature, guiding researchers who will conduct other studies, and having the potential to create intellectual resources.

2. MATERIAL and METHOD

Chemical Substances Used

Ethanol, Methanol, n-Hexane, Tetrahydrofuran (THF), Monopotassium hydrogen phosphate, Trichloroacetic acid, Hydrochloric acid, 2,4-Dinitrophenylhydrazine, Ethyl acetate, Guanidine-HCl, Carbon tetrachloride (CCl_4-simya, aldrich, catalogue No: 289116), Saffron (sigma, aldrich, catalogue No: S8381), Safranal (sigma, aldrich, catalogue No: W338907), Crocin (sigma, aldrich, catalogue No: 17304), Olive oil (sigma, aldrich, catalogue No:O1514), Ketamine hydrochloride.

Experimental Procedure

The rats used in the study were 54 Wistar albino breeds, weighing between 180 and 250 g. The experiment was carried out at Van Yüzüncü Yıl University, Experimental Medicine Research and Application Center Directorate. Rats provided in the same place were fed with standard pellet feed throughout the experimental period. The room temperature was adjusted to 22 ± 2 °C and the environment was adjusted to a 12-hour light-12-hour dark rhythm. Rats were kept in standard plastic cages with free food and water until the end of the experiment. Before starting the research, the study was approved by the Van Yuzuncu Yil University Ethics Committee with the decision dated 25.12.2015 and numbered 2015/560.

Establishment of experimental groups and experiment plan

Carbon tetrachloride was mixed with olive oil at a ratio of 1:1 and administered intraperitoneally as a single dose to the third, seventh, eighth and ninth groups on the 7th day as 1ml/kg. Safron was administred as oral gavage to the fourth and seventh groups at a daily dose of 100 mg/kg. Safranal was administered to the fifth and eighth groups and crocin intraperitoneally to the sixth and ninth groups at a daily dose of 100 mg/kg. The application in the groups created is stated below. Blood samples were taken from rats 24 hours after CCl_4 administration (day 8). The preparation method of CCl_4, saffron, safranal, and crocin substances, as well as the subsequent application procedure to rat groups, are stated above.

In the study, 9 groups were formed, with 6 rats in each group. 1) The control group was given saline (0.9% NaCl) orally for 7 days, 2) the olive oil group was administered (1 ml/kg i.p. olive oil) for 7 days, 3) the CCl_4 group was administered a single dose on the 7th day (1 ml/kg i.p.), 4) saffron group was applied for 7 days (100 mg/kg by orogastric gavage), 5) safranal group was applied for 7 days (100 mg/kg i.p.), 6) crocin group was administered for 7 days (100 mg/kg i.p.), 7) CCl_4 + saffron group (CCl_4 was administered as a single dose 1 ml/kg 1:1 on the 7th day; saffron was administered at 100 mg/kg by orogastric gavage for 7 days), 8) CCl_4 + safranal group (CCl_4 was administered as a single dose, 1 ml/kg i.p. on the 7th day; safranal was administered 100 mg/kg i.p. for 7 days), 9) CCl_4 + crocin group (CCl_4 was administered as a single dose, 1 ml/kg i.p. on the 7th day; crocin was administered at 100 mg/kg i.p. for 7 days).

Collecting Serum Samples

At the end of the study, the rats were anesthetized with 10% ketamine/Xylazine. The blood taken from the hearts of the rats with the help of injectors was put into gel biochemistry tubes. Serums were centrifuged at room temperature and 2500 rpm for 10 minutes to ensure appropriate separation and then stored at −65°C until the study began.

Protein Carbonyl Determination Method

The PCO content in the serum of rats was determined according to the method described by Reznick and Packer [9]. Briefly, 0.01M 2,4 – dinitrophenylhydrazine in HCl was added to rat

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serum. The resulting mixture was incubated for 120 minutes at room temperature, and then 1 ml of tricyclic antidepressants (TCA) was added. The samples were then incubated for 6 minutes and centrifuged for 15 minutes. The resulting mixture was washed with ethanol: ethyl acetate and dissolved in 0.02M phosphate buffer (pH=6.8). Each sample was scanned on Shimadzu UV-1800 spectrophotometer against a replica. Peak absorbance between 360-370 nm was used to quantify PCO and final data were recorded.

Determination of Vitamins (retinol, cholecalciferol, α-tocopherol and phylloquinone)

Preparing standard solutions for vitamins

Vitamins stock solutions were prepared at 500 µg/mL. The solutions were appropriately diluted with methanol to match the standard solution. Calibration was calculated using linear regression analysis of peak area to standard solution concentrations.

Extraction process

To prevent the samples from deteriorating against UV rays, they were thawed at ambient temperature under fluorescent lights and covered with plastic caps. The vitamins examined in the serum were extracted by modifying the method determined by Su et al. [21]. A 150 µL serum with 0.025% BHT was added to the extraction solution. Then, it was deproteinized by adding 150 µL EtOH and butylated hydroxytoluene (BHT), and the vortex mixed the samples. Samples were extracted twice with 800 µL *n*-hexane. The prepared samples were vortexed for 5 seconds and then centrifuged at 6000 rpm for 15 minutes. The hexane formed in the standard tube was evaporated to dryness under a stream of nitrogen at 36 °C. The residue formed at the bottom of the samples was dissolved in 0.05 mL of THF, and then 0.15 mL of methanol was added. After vortexing, the 0.1 mL samples for 1 minute, the samples were transferred to amber glass bottles.

Chromatographic conditions

The chromatographic system consisted of HP Agillent 1100 with a G-1328 Diode Array Detector (DAD) and G1329 ALS autosampler (-8 °C). Agilent Technologies HP software was preferred to process the data. 5 µm Gl Science C_{18} reverse phase column (250 × 4.6 mm ID) was used for separation. Then, the mobile phase of the MeOH-THF mixture (80:20, v/v) was made by modifying the method of Siluk et al. [22]. The pump used for vitamin analysis was set at a flow rate of 1.5 mL/min. Chromatographic analysis was made at 45°C using isocratic elution. The chromatogram was monitored with DAD array detection at 325, 265, 290 and 248 nm (simultaneous measurement of retinol, cholecalciferol, α-tocopherol and phylloquinone, respectively).

Statistical analysis

The results are presented as means ± the standard error of the mean (X±SEM). Variance analysis (ANOVA) was applied. Tukey's test was applied for post hoc comparison. Statistical significance was considered as $p<0.05$. The statistical analysis was done using SPSS®, version 23.0 statistical software (SPSS Inc. Chicago Ill, USA).

3. RESULTS

The PCO, retinol, cholecalciferol, α-tocopherol and phylloquinone data analyzed in rat serum within the scope of our study are shown in Table I. A comparison of PCO levels between groups is given in Figure 1. Considering the PCO data in the rat's serum, a statistically considerable ($p<0.001$) relationship was determined between the control and olive oil groups and the group administered 1 ml/kg CCl_4 (Table I). In addition, a significant relation was determined between the groups administered 100 mg/kg saffron, safranal and crocin, and the group administered 1 ml/kg CCl_4 ($p<0.01$) (Table I and Figure 1). The significant difference in PCO values between rat groups showed that the toxic effect of CCl_4 caused protein oxidation by creating oxidative stress in rats. It was observed that the application of saffron (100 mg/kg, oragastric gavage), safranal (100 mg/kg, i.p.) and crocin (100 mg/kg, i.p.) together with CCl_4 was significant on this oxidative stress (Figure 1).

Within the scope of our study, the levels of retinol, cholecalciferol, α-tocopherol and phylloquinone vitamins in serum between groups are shown in figures 2, 4, 6, and 8, and their chromatograms are shown in figures 3, 5, 7 and 9, respectively. It was determined that the vitamins in rat serum had significant content within the groups (except for the 3rd group, CCl_4 1 ml/kg i.p.) (Figures 2, 4, 6, 8). When the retinol vitamin was examined, a significant relationship was determined between the control, saffron (100 mg/kg, oragastric gavage) and olive oil (1 ml/kg i.p) groups and the group administered CCl_4 (1 ml/kg i.p), ($p<0.05$, $p<0.05$ and $p<0.01$, respectively) (Table I and Figure 2).

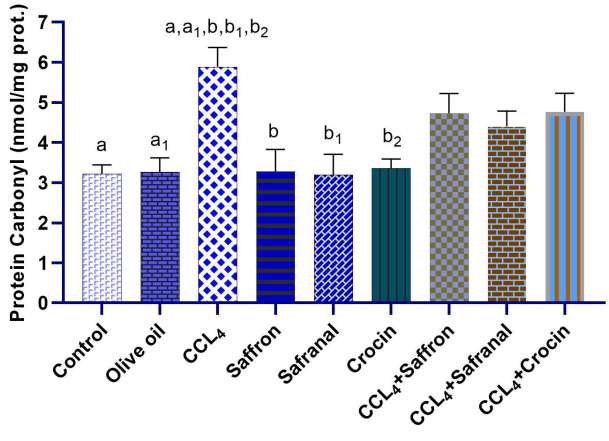

***Figure 1**. Comparison of PCO levels between rat serum of control, olive oil, CCl_4, saffron, safranal, crocin, CCl_4 + saffron, CCl_4 + safranal and CCl_4 + crocin groups.*

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***Table I**. PCO, retinol, cholecalciphenol, α-tocopherol, and phylloquinone findings in rat serum of control, olive oil, CCl_4, saffron, safranal, crocin, CCl_4 + saffron, CCl_4 + safranal and CCl_4 + crocin groups.*

Groups	PCO X ± SEM	Retinol X ± SEM	Cholecalciferol X ± SEM	α-tocopherol X ± SEM	Phylloquinone X ± SEM
Control	3.22±0.23^{a}	3.15±0,14^{c}	0.10±0.01b	1.30±0.23	0.23±0.03^{c}
Olive oil	3.27±0.35^{a1}	3.34±0,23^{b}	0.11±0.01^{c,a}	1.44±0.12	0.24±0.01^{c1}
CCl_4	5.89±0.48^{a,a1,b,b1,b2}	2.14±0.14^{c,b,c1}	0.06±0.00^{b,b1,a,a1}	0.89±0.13	0.12±0.00^{c,c1,c2}
Saffron	3.28±0.54^{b}	3.10±0.17^{c1}	0.11±0.00^{c1,a1}	1.28±0.13	0.22±0.03
Safranal	3.19±0.51^{b1}	3.04±0.22	0.10±0.00^{b1}	1.41±0.24	0.23±0.02^{c2}
Crocin	3.36±0.24^{b2}	2.99±0.35	0.10±0.00	1.35±0.26	0.21±0.04
CCl_4 + Saffron	4.73±0.49	2.76±0.19	0.08±0.00	1.00±1.16	0.17±0.00
CCl_4 + Safranal	4.41±0.38	2.86±0.15	0.09±0.00	1.13±0.21	0.18±0.02
CCl_4 + Crocin	4.77±0.46	2.54±0.17	0.07±0.00^{c,c1}	0.97±0.09	0.16±0.03

Different letters: significant, differences between groups (a: p<0.001, b: p<0.01, c: p<0.05). PCO (nmol/mg prot.), retinol, cholecalciferol, α-tocopherol and phylloquinone (μmol/L).

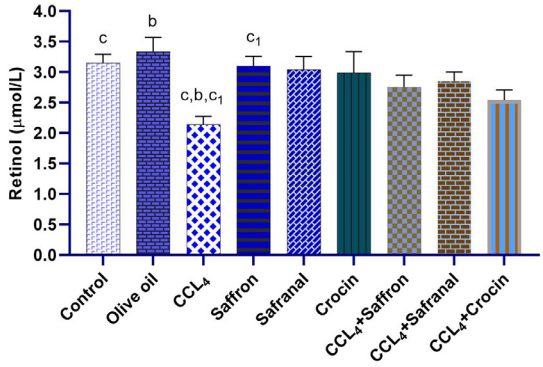

***Figure 2**. Comparison of retinol levels between rat serum of control, olive oil, CCl_4, saffron, safranal, crocin, CCl_4 + saffron, CCl_4 + safranal and CCl_4 + crocin groups.*

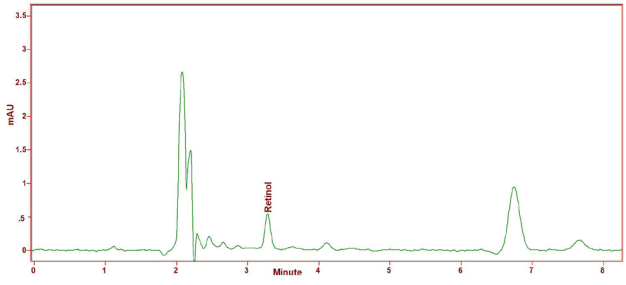

***Figure 3**. Chromatogram of the retinol (vitamin A) [(mobile phase: methanol/ tetrahydrofuran (20/80 v/v)], flow rate 1,5 mL min^{-1}. Clomn: GI science C_{18} 5μL (250/4,6 mm), wavelength: 325 nm.*

Considering the cholecalciferol data, a statistically significant relationship (p<0.05 and p<0.05) was determined between saffron and olive oil and the group treated with CCl_4 + crocin. On the other hand, a significant relation was found between the control, saffron, safranal and olive oil and 1 ml/kg CCl_4 administered group (p<0.01, p<0.01, p<0.001 and p<0.001, in order of) (Table I and Figure 4).

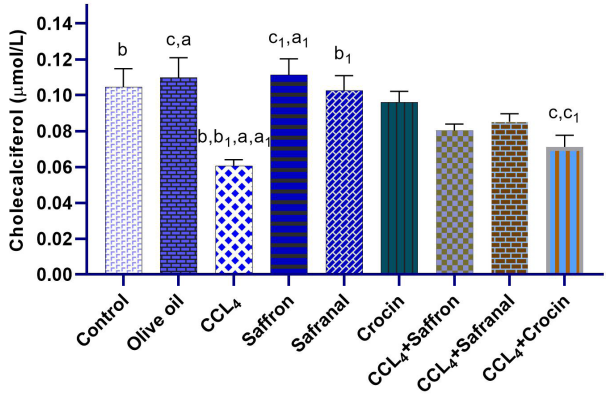

***Figure 4**. Comparison of colecalciferol levels between rat serum of control, olive oil, CCl_4, saffron, safranal, crocin, CCl_4 + saffron, CCl_4 + safranal and CCl_4 + crocin groups.*

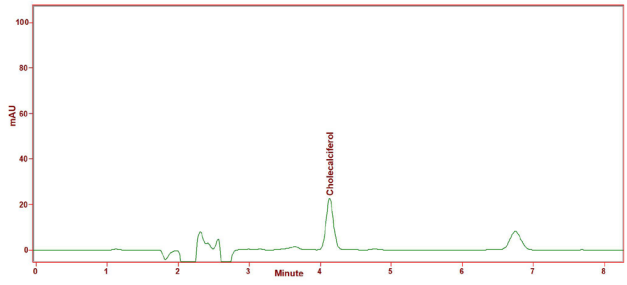

***Figure 5**. Chromatogram of the colecalciferol (vitamin D) [(mobile phase: methanol/ tetrahydrofuran (20/80 v/v)], flow rate 1,5 mL min^{-1}. Clomn: GI science C_{18} 5μL (250/4,6 mm), wavelength: 265 nm.*

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Within the study's scope, no statistically significant relationship was found between the groups in the level of α-tocopherol (p>0.05, data not shown, Table I and Figure 6).

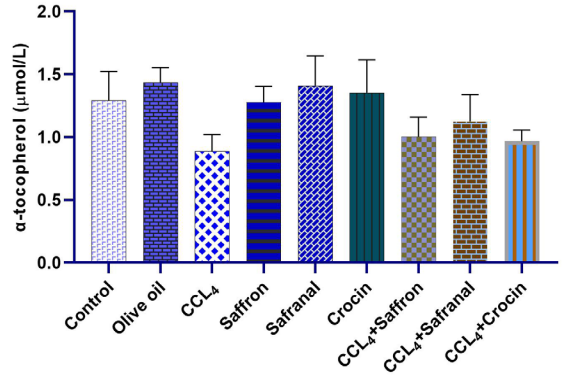

***Figure 6**. Comparison of α-tocopherol levels between rat serum of control, olive oil, CCl_4, saffron, safranal, crocin, CCl_4 + saffron, CCl_4 + safranal and CCl_4 + crocin groups.*

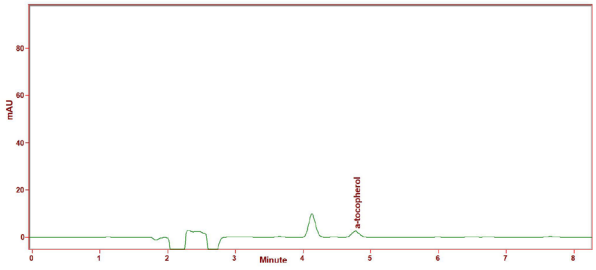

***Figure 7**. Chromatogram of the α-tocopherol (vitamin E) [(mobile phase: methanol/ tetrahydrofuran (20/80 v/v)], flow rate 1,5 mL min^{-1}. Clomn: GI science C_{18} 5µL (250/4,6 mm), wavelength: 290 nm.*

When the phylloquinone data were examined, a significant relationship was determined between the control (p>0.05), safranal (p>0.05), olive oil groups (p>0.05) and the CCl_4 group (1 ml/kg i.p) (Table I and Figure 8).

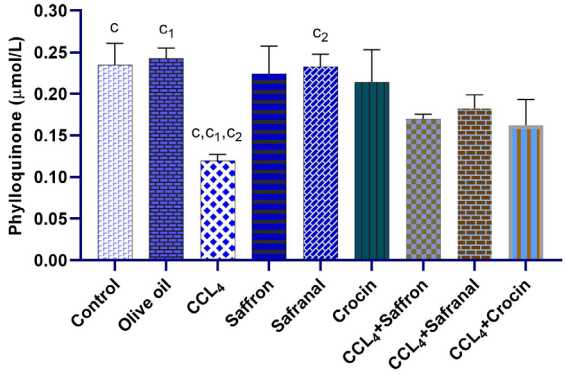

***Figure 8**. Comparison of phylloquinone levels between rat serum of control, olive oil, CCl_4, saffron, safranal, crocin, CCl_4 + saffron, CCl_4 + safranal and CCl_4 + crocin groups.*

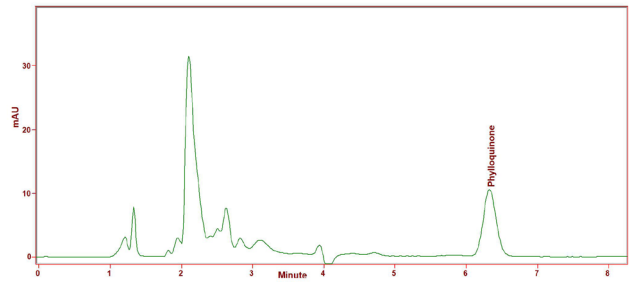

***Figure 9**. Chromatogram of the phylloquinone (vitamin K) [(mobile phase: methanol/ tetrahydrofuran (20/80 v/v)], flow rate 1,5 mL min^{-1}. Clomn: GI science C_{18} 5µL (250/4,6 mm), wavelength: 248 nm.*

4. DISCUSSION

Toxic effect of CCl_4: It is the result of activation of trichloromethyl (-CCl3) by cytochrome P450, which easily reacts with oxygen to form trichloromethylperoxy radical (CCl3OO.) These free radicals initiate cell damage through two main mechanisms: covalent bonding and lipid peroxidation [23]. Protein carbonyls levels increase when cells are exposed to various oxidative stress conditions [8]. CCl_4 is known in the literature to be a toxic chemical that causes cell and tissue damage in animals [1]. PCO is widely used as an early marker of protein oxidation in cells and tissues. One of the techniques used to detect proteins is the reaction of carbonyls with 2,4-denitrophenylhydrazine (DNPH) to form stable dinitrophenyl (DNP). Because DNP absorbs light at 370 nm, carbonyl groups can be measured spectrophotometrically.

Carbonyl groups enter proteins with various oxidative groups, especially metal ion-catalyzed variants of specific protein amino acid side chains. On the other hand, they are also incorporated by removing carbonyl-containing oxidized lipids (MDA, HNE) or sugars [24]. 4-hydroxyonenal (HNE) is in higher amounts in lipid peroxidation chain reactions due to increased oxidative stress. Although, protein oxidation's mechanism, pathways and products differ, factors that cause lipid oxidation can also initiate protein oxidation. Functional groups on the side chains of amino acid residues and the peptide backbone are targets for ROS. In this respect, PCO levels in the experimental groups focused on detecting carbonyl groups as markers of oxidative protein modification.

In the study, a single dose of 1 ml/kg CCl_4 was administered to the rats in the 3rd, 7th, 8th, and 9th groups on the 7th day and were sacrificed under anesthesia on the 8th day of the application. The purpose of this study was to determine the levels of PCO, retinol, α-tocopherol, cholecalciferol and phylloquinone in the serum of rats treated with CCl_4, saffron and saffron components (safranal and crocin), and to determine which of the important components of saffron and its components are more effective. The PCO, retinol, α-tocopherol, cholecalciferol and phylloquinone data measured in serum are given in Table I. According to the statistical analysis results in the study, a significant increase

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($p<0.001$) was detected in PCO levels between the control and olive oil groups and the CCl_4 group. On the other hand, there was a significant difference ($p<0.01$) between the CCl_4 group and the saffron, safranal and crocin groups. PCO results showed that CCl_4 caused oxidative damage, and the effect in the groups treated with carbon tetrachloride 100 mg/kg in saffron, safranal and, crocin was as close as in the control and olive oil groups. The presence of PCO, a high level of oxidative biomarker in CCl_4 administration, was evident in rats; CCl_4 caused, most likely, oxidative stress. From this point of view, it is evident that saffron protects against CCl_4-induced oxidative stress in rats, as assessed by the reduction in the formation of safranal and crocin protein carbonyl. On the other hand, no study has been found in the literature on the effect of saffron and its active ingredients, safranal and crocin compounds, on PCO in CCl_4 rats. From this perspective, it can be thought that these data will be a reference for similar studies.

It is impossible to have a life completely devoid of the oxidative stress that occurs in the cell due to free radicals. Ultimately, there will be a loss in all cells that produce energy, and minimizing the damage caused by this loss is a situation that the cell will overcome. So, how will cells do this? At this point, endogenous and exogenous antioxidants come into play in response to reactive oxygen species (ROS) [25]. People have been looking for medicine in nature to treat their diseases in the past, and this process continues. Due to the low side effects, difficulty of administration, and prices of synthetic drugs, it has been widely used worldwide [26]. The mechanisms of antioxidants, proteins and amino acids in foods have been associated with their ability to chelate pro-oxidant metals [27].

The saffron plant has been found to contain more than 150 volatile and aromatic compounds, including pharmacologically active and important components such as safranal, crocin, picrocrocin and crocetin [28-30]. Research showed that this plant has antioxidant potential, as shown by the results of in-vitro analysis performed on different parts of saffron flowers [31]. On the other hand, the literature reveals that saffron is used to treat diabetes, bronchitis, asthma, coronary artery diseases and neurodegenerative disorders [31-32]. Safranal, an important component of the essential oil contained in saffron, has been used in different scientific studies to evaluate pharmacological and biological activities since its discovery [26]. For example, in their study on mice in 2015 by Zanjani et al., it was found that safranal is safe for the immune system and has no toxicity on cellular immune responses. On the other hand, another study conducted by Boskabady et al., in 2014 found that safranal has therapeutic values in treating asthma with its immunoregulatory effect that reduces airway sensitivity [33-34]. Crocins are bioactive compounds and water-soluble carotenoids found in the stigmas of saffron, composed of their glycosides [28-30, 35]. This substance is the main factor for the bitter taste of bile and may be involved in the production of safranal [36].

Monaghan and Schmitt first described the antioxidant potential of vitamin A and carotenoids [37]. This is important, since, carotenoids are the precursors of vitamin A. It is thought that some of their specific functions, closely related to their functions in plants, are also effective in mammalian tissues [38]. α-tocopherol is a potent peroxyl (ROO-) radical scavenger, a chain-breaking antioxidant that prevents the propagation of free radical damage in biological membranes [39]. Due to this and similar studies, it is now a fact that vitamins such as α-tocopherol and carotenoids (including ß-carotenoid, the precursor of vitamin A) have antioxidant capacity. Although, the possible effects of vitamin K and D on oxidative stress have received little attention, their roles or deficiencies in the antioxidant defense system are poorly understood [40]. However, studies have identified vitamin D receptors in various tissues. Therefore, it has been suggested that vitamin D may play a role in cardiovascular, multiple sclerosis, hypertension, colorectal and prostate cancers, diabetes risk and cancer prevention [41, 42]. On the other hand, vitamin K is fat-soluble compound required for the post-translational conversion of protein-bound glutamates to γ-carboxyglutamates in various proteins, apart from its function in coagulation. Studies on the effect of vitamin K on protein carbonyl have been reported [35]. The 1,4-naphthoquinone structure of vitamin K is similar to the benzoquinone structure, and therefore, these vitamins may also contain antioxidant properties [43]. Conversely, dietary vitamin deficiency or insufficiency affects changes in serum protein levels. Serum vitamin levels may provide important parameters in neutralizing free radicals. When living tissue is under stress, PCO can be found in higher amounts due to the increase in the chain reaction [44]. The decrease or increase in both PCO and vitamin levels may give clues about the effect of antioxidants.

When the retinol, cholecalciferol, α-tocopherol, and phylloquinone levels were examined according to the results of the statistical analysis in the study, retinol, cholecalciferol and phylloquinone levels, a significant decrease was determined between CCl_4 and control group ($p<0.05$, $p<0.01$, $p<0.05$) and between CCl_4 and olive oil group ($p<0.01$, $p<0.001$, $p<0.05$), respectively. In addition, a significant decrease was observed in retinol and cholecalciferol values between CCl_4 and saffron group ($p<0.05$, $p<0.001$), and a significant decrease in cholecalciferol and phylloquinone levels between CCl_4 and safranal groups ($p<0.01$, $p<0.05$). However, there was a significant decrease ($p<0.05$, $p<0.05$) in cholecalciferol levels between olive oil and CCl_4 + crocin and saffron and CCl_4 + crocin groups. As it is known, vitamins A, D, E and K are stored in the liver and fatty tissues. It allows the body to benefit from these stored reserves when insufficient dietary intake. These vitamins are essential for antioxidant defense and many other functions [45]. The study conducted by Ynaci et al., determined that α-tocopherol was effective in healing liver damage due to CCl_4 application to rats [46]. In addition, against the liver damage caused by the increased release of ROS, Elsisi et al., in their study, found that liver damage was blocked in rats treated with 250,000 IU/kg/day retinol against 0.15 or 2 ml/kg CCl_4 challenge [47]. On the other hand, in the study conducted by Forbes and Taliaferro, they concluded that diet-fed rats were more resistant to the hepatotoxic effects of carbon tetrachloride than animals fed a well-balanced stock diet or a low vitamin D but otherwise balanced diet [48]. Our study evaluated the vitamins and PCO levels of saffron and its active ingredients against CCl_4

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challenge without any external vitamin supplements in rats. It was observed that oxidative stress increased in rats exposed to CCl_4 and, in parallel, PCO, retinol, cholecalciferol, α-tocopherol and phylloquinone levels increased. The increased presence of vitamins along with PCO, a protein oxidation marker, indicates that these vitamins have antioxidant properties. However, more studies are needed on the antioxidant properties of these vitamins and their presence in oxidative stress. On the other hand, when the levels between the groups were examined, it was determined that 1 ml/kg CCl_4 + 100 mg/kg safranal group showed significant difference compared to the saffron and crocin groups. It can be said that this is due to the bitter taste and aroma of safranal and its positive benefits to the vitamins in the antioxidant defense system. Recent studies have shown that safranal is the part of saffron that determines its most important characteristic flavour [49]. It has been shown to have antioxidant effect due to its high radical scavenging activity [50].

Conclusion

Our study observed that oxidative stress increased in rats exposed to CCl_4 and, in parallel, PCO, retinol, cholecalciferol, α-tocopherol and phylloquinone levels increased. When the levels between the groups were examined, it was determined that 1 ml/kg CCl_4 + 100 mg/kg safranal group showed significant difference compared to the saffron and crocin groups. In this case, it can be said that the bitter taste and aroma of safranal are effective. As a result, saffron and safranal have a protective effect against the oxidative damage caused by CCl_4 on protein carbonyl, retinol, phylloquinone and cholecalciferol, and this effect may be due to the strong antioxidative effects of saffron and safranal. Saffron is an important plant that has been subject to application on laboratory animals. Its effective application in both medicine and alternative medicine has attracted the attention of many researchers. This attention is mostly due to the reporting of the effects of saffron on antitumor and anticancer. However, studies in which this plant and its active ingredients are applied together are limited. No study in the literature is close to the vitamins (A, D, E, K) and PCO values between the groups in our experimental study. In this respect, it can be said that this experimental study will contribute to the literature and attract attention.

Compliance with Ethical Standards

Ethical approval: This study was approved by Van Yuzuncu Yil University Animal Research Ethics Committee with the decision dated 25.12.2015 and numbered 2015/560.

Conflict of interest: The authors declare that there is no conflict of interest.

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Authors contributions: IA, IB and GO: Collected the material, AB and DY: Performed the experiments, AB: Analyzed and interpreted the results and wrote the paper, SE: performed the statistical analysis and supervised the manuscript. All authors approved the final version of the manuscript.

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Canal to calcar ratio is associated with lumbar compression fractures

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ABSTRACT

Objective: Osteoporosis is one of the major public health problems. Singh (SI) and Genant indexes are the most well-known osteoporosis evaluation methods. Femoral cortical thickness index (CTI) and femoral canal to calcar ratio (CCR) values have been found to be more informative in the literature. This study aimed to investigate the relationship between SI, CTI, CCR, bone mineral density, and blood tests.

Patients and Methods: Hospital digital archives were searched and postmenauposal female patients who underwent bone scanning between 2018 and 2020 were included. Demographic data, blood laboratory and bone mineral densitometry (BMD) test results, and radiographic views were collected. The results were statistically analysed and expressed as mean ± standard deviation.

Results: The mean age was 66.14±6.82 years. There were 22 patients with lumbar compression according to Genant criteria. Also, 52 patients had osteoporosis and 35 patients had osteopenia according to the spine or hip BMD T scores. CCR was found to be significantly related to lumbar compression (p=0.04).

Conclusion: In this study, no correlation was found between CCR value and T score. However, CCR value was found to be associated with lumbar vertebral compression, which is helpful in the diagnosis of osteoporosis. It may be considered as a parameter that should be studied more in the diagnosis of osteoporosis.

Keywords: Osteoporosis, Canal to calcar ratio, Singh Index, Cortical Thickness Index, Lumbar compression

1. INTRODUCTION

Osteoporosis is one of the major public health problems. As the elderly population increases, osteoporosis-related fractures become more common [1]. The hip and spine are the most affected sites. Bone mineral densitometry (BMD) is the gold standard to identify this situation [2]. As osteoporosis is related to perioperative and postoperative technical complications, it is important to identify it for better surgical results [3, 4]. However, bone densitometry is more expensive than radiography, and x-ray devices are more common in healthcare centers. An easier and cheaper method to diagnose osteoporosis is needed and Singh index (SI) is a well-studied parameter that revealed different results about osteoporosis in literature. SI was published in 1970 and several studies have examined the reliability and validity of this method. Although, it is a cheap and easy method, there are controversial results about its reliability and validity in predicting osteoporosis compared to BMD in relevant literature and it was described as unreliable due to low rates in interobserver evaluations [5]. These controversial results lead investigators to find more reliable radiologic methods to compare with the current gold standard method, dual-energy x-ray absorptiometry (DEXA). Genant index (GI) is one of the most well-known and frequently used radiologic methods focusing on the spine, while SI focuses on the hip [6, 7]. Genant's index is based on vertebral body compression, which shows osteoporotic vertebral fractures [7]. Femoral cortical thickness index (CTI) and femoral canal to calcar ratio (CCR) were found to be more informative in the literature [8]. CCR and CTI are two radiologic methods first described by Dorr et al [9]. Although, these indices were primarily designed to select the correct prosthetic design for the hip (cemented or cementless femoral stem) preoperatively, they also reflect the osteoporotic morphological changes.

Lumbar compression fractures and their sequels are significant causes of back pain and disability in osteoporotic patients.

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This study investigated the association between osteoporotic lumbar compression fractures and osteoporotic, radiologic, and laboratory parameters and aimed to reveal the possible relationship between osteoporosis and radiological parameters.

Table I. *Description of Singh and Genant's Indices [6-7]*

	Singh Index
Grade	**Description**
1	Even the principal compressive trabeculae are markedly reduced in number and are no longer prominent
2	Only the principal compressive trabeculae stand out prominently, the others have been more or less completely resorbed.
3	There is a break in the continuity of the principal tensile trabeculae
4	Principal tensile trabeculae are markedly reduced in number but can still be traced from the lateral cortex to the upper part of the femoral neck
5	The structure of principal tensile and principal compressive trabeculae is accentuated. Ward's triangle appears prominent
6	All the normal trabecular groups are visible and the upper end of the femur seems completely occupied by cancellous bone.
	Description of Genant Index
Grade	**Description**
0	Normal
1	Mildly deformed (approximately 20-25% reduction in anterior, middle, and/or posterior height and a reduction of area 10-20%)
2	moderately deformed (approximately 25-40% reduction in any height and a reduction in area 20-40%)
3	severely deformed (approximately 40% reduction in any height and area)

2. PATIENTS and METHODS

The Study Population

Hospital digital archives were searched retrospectively between July 2018 and March 2020. The study was conducted in accordance with the Principles of the Declaration of Helsinki and was approved by the Kahramanmaras Sutcu Imam University Ethics Committee (date: 18.03.2020, approval number: 2020/06). Postmenauposal female patients with DEXA, lumbar, and pelvic x-rays, and comprehensive laboratory tests were included. The patients with missing data, acute lumbar and hip fractures for less than 6 months, rheumatologic diseases, and malignancies, were excluded. Patients with previous hip surgery, spine surgery, deformity of the proximal femur, and metabolic bone disease were excluded.

Data Source

Picture Archiving and Communication Systems (PACS) and hospital archive files were examined. Demographic data, blood test results, DEXA results, and radiographic views were collected. A total of 95 patients were included. BMD and T scores were measured by DEXA scan of the femoral neck and lumbar spine (Primus, Osteosys, Seoul, South Korea). Blood tests of blood calcium, phosphorus, and creatinine were collected. Direct radiographic views of the anteroposterior (AP) pelvis, AP, and lateral views of lumbar views were examined. CCR, CTI, and SI were calculated from the pelvis AP view as done previously in the literature (Figure 1) [6, 8]. SI and GI are described in Table I. GI was calculated from lumbar radiography as done previously in the literature [7]. GI of grade 1 and above is described as a lumbar compression fracture.

Table II. *Mean values, standard deviations, and p values of groups with or without lumbar compression*

	Patients with Lumbar Compression (N:22)	**Patients without Lumbar Compression (N:73)**	**P Value**
Singh Index	4.36±1.78	4.82±1.44	0.344
CCR	0.74±0.09	0.70±0.08	**0.04***
CTI	0.50±0.06	0.52±0.06	0.093
Age	68.14±5.71	65.57±7.04	0.135
Calcium (Mg/Dl)	9.49±0.52	9.59±0.45	0.292
Phosphorus (Mg/Dl)	3.27±0.51	3.46±0.58	0.216
Creatinin (Mg/Dl)	0.72±0.08	0.76±0.15	0.582
Lumbar BMD (gr/cm^2)	0.96 ± 0.12	0.99±0.18	0.158
Lumbar T Score	-1.61±1.60	-1.15±1.36	0.105
Femoral Neck BMD (gr/cm^2)	0.90±0.29	0.90±0.25	0.608
Femoral Neck T Score	-2.29±1.70	-2.36±0.97	0.555
BMI(Kg/M^2)	33.04±6.52	32.33±5.44	0.757
Weight (Kg)	77.50±15.51	76.28±13.57	0.569

*Data shown as mean ± standard deviation or n (%). *(p<0.05). CCR: Canal to Calcar Ratio, CTI: Cortical Thickness Index, BMD: Bone Mineral Density, BMI: Body Mess Index*

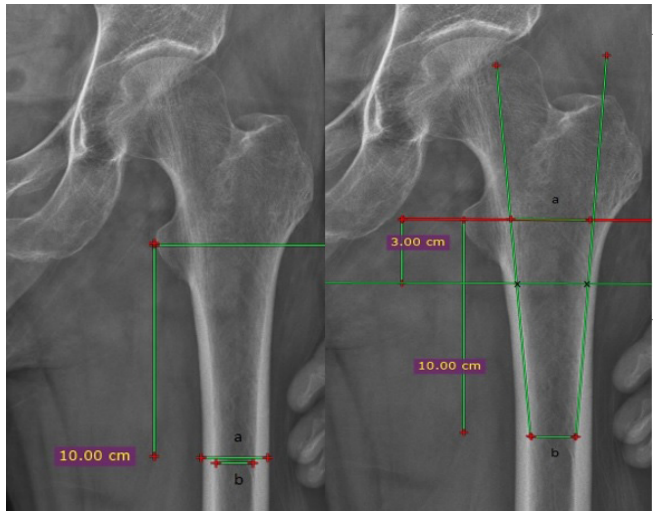

Figure 1. *Cortical Thickness index (CTI): (a-b)/a on the left, Canal to Calcar Ratio (CCR): b/a on the right*

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Statistical Analysis

Radiographic measurements, demographic data, and laboratory results were evaluated statistically, and the results were expressed as mean ± standard deviation (SD). The suitability of the quantitative data to the normal distribution was analyzed with the Single Sample Kolmogorov-Smirnov test. Either Student's t-test or Mann Whitney-U test was used according to distribution. The Chi-square test was used to compare categorical data between groups. Either Spearman correlation coefficient (rs) or Pearson's correlation coefficient was used to evaluate the relationship between variables depending on the distribution of variables. Finally, ROC curve analysis was performed to determine each radiographic measurement method's threshold values, sensitivity, and specificity. SPSS 22.0 software was used for analysis. P-value <0.05 was considered statistically significant.

Table III. *Mean values, standard deviations, and p-values of groups with or without osteoporosis and osteopenia*

	Patients with osteoporosis (N:52)	Patients with osteopenia (N:35)	Patients without osteoporosis or osteopenia (N:8)	P value
Singh Index	4.44±1.66	4.91±1.40	5.63±0.51	0.144
CCR	0.71±0.09	0.70±0.08	0.70±0.12	0.989
CTI	0.51±0.06	0.53±0.06	0.52±0.05	0.576
Age	66.78±6.50	66.82±6.28	59.12±7.93	0.038
Calcium (Mg/Dl)	9.59±0.54	9.46±0.33	9.92±0.30	0.009
Phosphorus (Mg/Dl)	3.48±0.55	3.29±0.54	3.57±0.78	0.308
Creatinin (Mg/Dl)	0.74±0.12	0.78±0.16	0.70±0.04	0.192
Lumbar BMD (gr/cm^2)	0.917 (0.18)*	0.994 (0.10)*	1.150 (0.21)*	0.0007**
Lumbar T Score	-1.75±1.37	-0.85±1.32	0.05±0.84	0.001***
Femoral Neck BMD (gr/cm^2)	0.603 (0.01)*	0.774 (0.01)*	0.873 (0.01)*	< 0.0001**
Femoral Neck T Score	-2.99±0.96	-1.82±0.57	-0.52±1.35	<0.001***
BMI(Kg/M^2)	33.04±6.52	32.33±5.44	36.47±4.69	0.007***
Weight (Kg)	72.02±13.20	80.80±13.28	87.50±10.74	0.002***

*Data shown as mean ± standard deviation or n (%). * Median (interquartile range) ** Mann-Whitney u test (p<0.05). ***Student's T test (p<0.05). CCR: Canal to Calcar Ratio, CTI: Cortical Thickness Index, BMD: Bone Mineral Density, BMI: Body Mess Index*

3. RESULTS

The power of the study was calculated as 61% by considering the 5% error rate of the post hoc power analysis method based on the averages of CCR of the groups containing a total of 95 subjects. The mean age was 66.14±6.82. There were 22 patients with lumbar compression according to the Genant criteria. Also, 52 patients had osteoporosis and 35 patients had osteopenia according to the spine or hip BMD T scores. Mean T scores for hip and spine were – 2.3 ± 1.17 and – 1.2 ± 1.43 respectively.

Patients were divided into two groups considering the presence of lumbar compression. SI, CTI, CCR, age, Ca, P, Creatinin, Lumbar T score and BMD, Femoral neck T score and BMD, body mass index (BMI), and weight values of both groups are presented in Table II.

Patients were divided into three groups due to the T score value of either the lumbar or femoral neck area. Patients with T score values below – 2.5 were defined as patients with osteoporosis, whereas patients with T score values between – 2.5 and – 1 were defined as osteopenia. SI, CTI, CCR, Age, Ca, P, Creatinin, Lumbar T score, and BMD, Femoral neck T score and BMD, BMI, and weight values of all groups are presented in Table III.

Correlation analysis released a significant correlation of vertebral compression with calcar to canal ratio (r: 0.212,p: 0.039). ROC analysis revealed that a CTI value less than 0.51 does not significantly indicate the presence of lumbar compression with 63.6% sensitivity, and 63% specificity but a CCR value of more than 0.71 indicates the presence of lumbar compression with 59.1% sensitivity, 57.3% specificity (Table IV).

Table IV. *ROC analysis results of CCR and CTI*

Variable	Cutoff value	The area under the curve (95% confidence interval)	Sensitivity (%)	Specificity (%)	P value
CCR	0.71	0.645 (0.516-0.774)	59.1	57.3	0.040
CTI	0.51	0.619 (0.482-0.755)	63.6	63.0	0.093

CCR: Canal to Calcar Ratio, CTI: Cortical Thickness Index

4. DISCUSSION

In this study, the SI and laboratory parameters were found to be unrelated to osteoporosis as reported in previous studies [10, 11]. Although, SI scores were lower in the osteopenic and osteoporotic patient groups, they did not show a significant difference. On the other hand, CCR was found to be significantly higher in patients with lumbar compression (p=0.04) and significantly correlated with lumbar compression. Although, the CCR index was primarily described for proximal femoral morphology, it did not reveal any significant difference with osteoporosis and any correlation with femoral T neck scores in this study. Also, it was shown that CCR more than the cut-off value of 0.71, significantly indicated lumbar compression with 59.1% sensitivity and 57.3% specificity. Lumbar compression occurs as a result of osteoporosis and is known to significantly increase the lumbar spine bone density [12]. Therefore, it may be told that osteoporosis of the spine can give correct results with a T-score only at the period before compression happens, which

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we believe will explain this contradictive result. However, a prospective study with more patient data will give more accurate results. The cortical thickness index (CTI) did not reveal any significant difference with any osteoporotic parameter in this study. However, there are different results in the literature. Köse et al., found a significant relationship between osteoporosis with CCR and CTI [8]. Sah et al., found CCR not to be related to the T score, but CTI showed a significant relation [11]. Yun et al., and Yeung et al., found CTI to be significantly related to the DEXA score [13, 14]. The threshold values of CCR in this study for predicting vertebral compression were 0.71 with 59.1% sensitivity and 57.3% specificity. Although, this cut-off value was significant, these values need to be proved by further studies, especially by prospective randomized trials. Since, vertebral compression is one of the signs of osteoporosis and CCR significantly predicts lumbar vertebral compression in this study, CCR may be used to predict osteoporotic lumbar vertebral compression fracture risk.

Osteoporosis is considered a metabolic bone disease in which the balance between bone formation and resorption is disrupted. For diagnosis and treatment, it is necessary to investigate bone metabolism and the affecting factors. Certain laboratory tests are required to diagnose and monitor each patient's treatment. Routine laboratory findings in patients with primary osteoporosis are usually within normal limits [15]. Serum calcium exists in three different fractions protein-bound form, ionized form, and phosphate, sulfate, and bicarbonate complexes. Total Ca is ordinarily used in clinical evaluation. In this study, it is found that blood calcium results were significantly lower in osteoporotic and osteopenic patients; however, all results were at normal levels.

This study found that BMI and weight were significantly higher in a group of patients without osteoporosis or osteopenia. Nevertheless, the mean BMI values of all groups were obese (>30). Increased fat mass is thought to have negative effects on bone mineral density [16]. Decreased physical activity is often associated with obesity and that could contribute to a decrease in bone mass. Although, body mass has a positive effect on bone formation, it remains controversial whether mass obesity is beneficial to the bone. The underlying pathophysiological relationship between obesity and bone is complex; this result could be an example.

There were some limitations of this study. A small number of patients was included in this study. Moreover, low thoracic vertebra fractures which are common in patients with osteoporosis were not investigated in this study. The fact that all patients were postmenopausal women, that gender discrimination was made, and that premenopausal patients were omitted prevents the generalization of the population. The study design was retrospective and, therefore prone to bias. The omission of FRAX in our analysis is another limitation. The FRAX score integrates multiple clinical risk factors and BMD measurements to provide a comprehensive fracture risk assessment [17]. Including a comparison with FRAX would have enriched our study by offering a broader perspective on the predictive value of CCR in the context of established fracture risk assessment tools. Although, this study was from a secondary healthcare center with a more homogenous patient group, a prospective study with a large number of patients and including both genders is needed for more accurate results.

Conclusions

CCR was found to be associated with lumbar vertebral compression fractures. It can be considered a helpful tool in diagnosing lumbar osteoporosis. Although, the CCR value was not found to be associated with the lumbar or femoral neck T score in this study, it can be seen as a parameter that needs to be studied more in the diagnosis of osteoporosis, since, significant results were obtained in previous studies showing this relationship.

Compliance with Ethical Standards

Ethics committee approval: This study was pproved by Kahramanmaras Sutcu Imam University Ethics Committee (date: 18.03.2020, approval number: 2020/06). The study was conducted in accordance with the Declaration of Helsinki. Both oral and written informed consent was obtained from the patients.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors contributions: EI**:** Idea/Hypothesis, EI: Design, EI: Data collection/Data processing, EI and EI: Data Analysis, EI and EI: Preparation of the article. Both authors approved the final version.

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Effects of extracorporeal photopheresis on survival in chronic graft versus host disease

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ABSTRACT

Objective: Chronic graft versus host disease (cGVHD) develops after allogeneic hematopoietic cell transplantation, when immune cells from a non-identical donor initiate an immune reaction against the transplant recipient. Extracorporeal photopheresis (ECP) can be used in combination with prednisone in steroid-resistant cGVHD. In this study, the effect of ECP use on survival in cGVHD was examined.

Patients and Methods: Twenty-six patients who were followed up in the adult Hematology Clinic of Inonu University Turgut Ozal Medical Center for cGVHD were included in the study. Stem cell transplantation and ECP application parameters that may affect the survival of the patients were examined.

Results: The degree of involvement in cGVHD affects survival. Involvements with clinical and laboratory scores of 2 and above according to the National Institutes of Health consensus criteria, significantly reduced survival. The development time of cGVHD was found to be associated with survival, and that it had a positive impact on survival, especially when the disease developed after 220 days after the transplantation. It was observed that steroid dose taken during ECP, patient age and cGVHD prophylaxis used affected survival.

Conclusion: The use of ECP may be effective in survival, especially, in patients who develop cGVHD, 220 days after allogeneic transplantation. Concurrent use of steroids with ECP affects survival.

Keywords: Graft versus host disease, Allogeneic hematopoietic cell transplantation, Extracorporeal photopheresis, Survival

1. INTRODUCTION

Graft versus host disease (GVHD) can develop after allogeneic hematopoietic cell transplantation (HCT) when T cells from the donor initiate an immune reaction against the transplant recipient. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) can be differentiated by clinical manifestations. The National Institutes of Health (NIH) consensus criteria are the criteria accepted by many bone marrow transplant centers in the definition and follow-up of cGVHD. GVHD may sometimes be encountered by the clinician as an overlapping syndrome where acute and chronic features are intertwined [1].

The onset of cGVHD is typically ≥3 months after transplant. Nearly all cases occur within the first year after transplant, but in some cases, cGVHD can occur months or even years after HCT. Previously, the distinction between aGVHD and cGVHD was based on baseline <100 days and ≥100 days after transplantation, respectively. However, these conditions are no longer defined by the onset time after transplantation, but by their clinical and pathological features, both syndromes may occur outside of these time periods [2].

Chronic graft versus host disease is a clinical entity that mimics rheumatologic disorders (eg, scleroderma, Sjögren's disease, primary biliary cirrhosis, bronchiolitis obliterans). It may affect many systems of the body and may have a limited involvement. It is manifested by skin lesions, mucositis, increased liver function tests, dry mouth and respiratory complaints [3]. Higher degree of human leukocyte antigen incompatibility, older donor or recipient, transplantation from a female donor to a male recipient, history of pregnancy or transfusion in the donor, use of peripheral blood stem cell grafts, application of non-irradiated donor buffy coat transfusions, splenectomy

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of the recipient, cytomegalovirus (CMV), Epstein-Barr virus (EBV) seropositivity in the donor or recipient are major risk factors for the development of cGVHD [4,5].

There are more than 100 synthetic derivatives of psoralen used in extracorporeal photopheresis (ECP) [6]. When psoralen is exposed to UVA rays at a wavelength of 320-400nm, it forms the C4 psoralen-thymine compound, which binds to DNA pyrimidine bases [7]. In addition to blocking DNA synthesis, its reactivity to lipid membranes and cell elements contributes to cellular cytotoxicity [8].

Extracorporeal photopheresis occurs by collecting peripheral lymphocyte cells with an apheresis device, adding 8-methoxypsoralen to the product and transferring the new product formed as a result of exposure to ultraviolet rays [9]. ECP is an effective method in the treatment of patients with steroid-refractory cGVHD. In one third of the patients using steroids, steroid use is considerably reduced.

Extracorporeal photopheresis effectiveness is reduced if the patient has extensive involvement of cGVHD, thrombocytopenia, and if aGVHD has developed beforehand [10]. Contraindications for ECP are as follows: Psoralen sensitivity, photosensitivity, pregnancy, lactation, low complete blood count parameters (WBC<1.000mm3 / Platelet <20.000mm3 / Htc<28%), uncontrolled systemic infection, absence of lens (aphakia), history of heparin-induced thrombocytopenia, hemodynamic disorder. ECP administration should be avoided in patients with severe cardiovascular or renal impairment [11]. In this study, it was aimed to examine the parameters affecting survival in bone marrow transplant patients with cGVHD.

2. PATIENTS and METHODS

Study design

Adult patients (over 18 years of age) who had allogeneic bone marrow transplantation and developed post transplant cGVHD between January 2009-February 2022 were included in this study after institutional ethical approval.

Parameters that may affect survival, such as demographic data, donor characteristics, stem cell source, how long after a bone marrow transplant, cGVHD develops, preparation for transplantation, organs involved in cGVHD, cGVHD degree, ECP administration, steroid administration, cGVHD response assessment, patient follow-up time were examined. Data were analyzed retrospectively.

Response evaluation after ECP

National Institutes of Health (NIH) consensus criteria were used to evaluate patients' response [12]. For each organ or site (the skin, nails, scalp and body hair, mouth, eyes, genitalia, gastro intestinal tract, liver, lung, muscles/fascia/joints, hematopoietic and Immune) disease severity was graded with the degree of involvement between 0-3. Mild cGVHD (1 or 2 organs involved with no more than score 1 plus, Lung score 0), Moderate cGVHD (3 or more organs involved with no more than score 1 or at least 1 organ (not lung) with a score of 2 or Lung score 1), Severe cGVHD (At least 1 organ with a score of 3 or Lung score of 2 or 3). The response rate of the patients (complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), progression of disease (PD) was decided by examining differences between the grades.

Extracorporeal photopheresis procedure details

Extracorporeal photopheresis procedure was applied after the jugular or femoral catheters were inserted. The treated patients were using steroids (1-2 mg/kg/day). After collecting an average of 100 ml of mononuclear cells from the patient with the Spectra Optica Apheresis System (terumobct serial no: ip 07554 Atasehir/Istanbul), the collected product was placed in macrogenic sets (Macogenic Set, Mouvaux, France) and saline was added as much as the collected product. The amount of methoxypsoralen (micrograms) was calculated (amount of product collected X 0.017) and added to the collected product set. The product, which came to the final stage, was infused into the patient in minutes after being processed in the macogenic extracorporeal photopheresis device (Macopharma, Mouvaux, France) for an average of 8-10 minutes. The procedure was repeated once a week for an average of at least 4 weeks for each patient.

GVHD prophylaxis regimens

a.Methotrexate plus calcineurin inhibitor in transplants involving an HLA-matched sibling/relative donor. Antithymocyte globulin was added to methotrexate plus a calcinin inhibitor in transplants using a matched unrelated donor (i.e. ≥9/10 or ≥7/8 HLA alleles). **b**.Calcineurin inhibitor plus mycophenolate mofetile in haploidentical transplants. Post transplant cyclophosphamide was added. GVHD prophylaxis was performed using myeloablative conditioning calcineurin inhibitor plus methotrexate. **c**.Non-myeloablative conditioning regimens. In non-myeloablative or reduced-intensity conditioning (RIC), calcineurin inhibitor plus mycophenolate mofetil was administered.

Bone marrow conditioning regimens

In our center, busulfan/cyclophosphamide (Bu/Cy) for acute myeloid leukemia (AML), Bu/Cy for all or Cy/total body irradiation (TBI) preparation regimen was used in young patients under 40 years of age without comorbidities. Fludarabine (Flu)/Cy plus antithymocyte globulin (ATG) was used for apilastic anemia. BEAM for lymphomas and Bu/Cy/etoposide (E) regimens for non-hodgin lymphomas were applied. Bu/Flu/ATG was frequently used in the reduced-intensity conditioning (RIC) protocol.

Ethical consent

The study carried out by the adult Hematology Clinic of the Turgut Ozal Medical Center was approved by the Non-interventional Clinical Research Ethics Committee of Inonu University, Faculty of Medicine (date: 26.04.2022, approval number 2022/3326).

Statistical evaluation

Statistical analysis was performed using the SPSS (Windows software version 26.0 (IBM Corp., Armonk, NY, USA). Mann-Whitney U test and Pearson's chi-square test were used in the comparison of groups. Chi-square test and Fisher's exact test were used in the analysis of categorical variables. Categorical data were given as percentage. Quantitative variables were given as mean, standard deviation, median. Hazard ratio was calculated by Cox regression analysis. Follow-up period of the patients was determined as the time from bone marrow transplantation to the death of the patient. P values less than 5% were accepted as positive in the tests.

3. RESULTS

The data of 26 patients who developed cGVHD after allogeneic stem cell transplantation were evaluated. The mean age was 36.27 (± 13.82) years (10 (38.5%) women, 16 (61.5%) men). The descriptive and demographic data of the patients are shown in Table I.

Table I. ***Chronic graft versus host disease demographic data***

		Event				P
		Alive		Dead		
		n (%)	Median (Min-Max)	n (%)	Median (Min-Max)	
Sex	Female	5 (38.46)		5 (38.46)		1
	Male	8 (61.53)		8 (61.53)		
Age			26 (20-64)		45 (23-57)	0.044*

*Min-Max: Minimum-Maximum, * Statistical significance*

In the survival analysis of the patients, two groups were defined as alive (n=13) and deceased (n=13) (total=26). The mean survival time of the patients was 31.96±7.33 months, the 1-year survival rate was 53.6% and the 2-year survival rate was 47.6%. Figure 1 shows the survival curve of the patients.

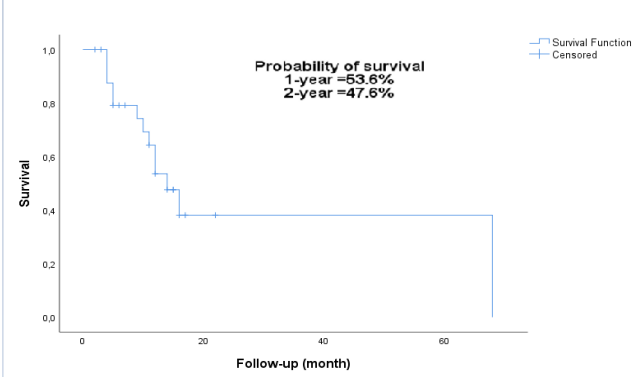

Figure 1. *Survival curve for cGVHD patients*

A statistically significant difference was found in cGVHD in terms of donor proximity (p=0.047), duration of cGVHD after transplantation (p= 0.006), ECP 1st month response (p= 0.03), and the last follow-up of the patient after ECP. The degree of involvement in cGVHD affected survival (p=0.097).

The degree of involvement in cGVHD was found to be 84.61% of patients with Grade ≤2 and 15.38% of patients with Grade >2. The survival of cGVHD patients with grade 2 and higher involvement was significantly reduced.

The duration of cGVHD development after transplantation was found to affect survival, and cGVHDs that developed after 220 days were found to have a positive effect on survival. Survival of the patients who developed cGVHD after 220 days or more was calculated as 84.61%. The percentage of mortality was 23.07.

No statistically significant correlation was found between the first week and 1st month response evaluation of ECP use and cGVHD (Table II).

Table II. *Statistical analysis of descriptive data in chronic graft versus host disease*

		Event		P
		Survived	Deceased	
		n (%)		
PRIMARY DISEASE	AML	6 (46.2)	8 (61.5)	0.48
	ALL	3 (23.1)	2 (15.4)	
	HODGKIN'S LYMPHOMA	0 (0)	0 (0)	
	NON-HODGKIN'S LYMPHOMA	0 (0)	1 (7.7)	
	APLASTIC ANEMIA	0 (0)	0 (0)	
	MDS	2 (15.4)	0 (0)	
	MULTIPLE MYELOMA	0 (0)	0 (0)	
	OTHERS	2 (15.4)	2 (15.4)	
DONOR FEATURE	MATCH (8/8)	12 (92.3)	13 (100)	1
	MISMATCH (7/8)	0 (0)	0 (0)	
	MISMATCH (≤6/8)	1 (7.7)	0 (0)	
DONOR KINSHIP	RELATIVE	10 (76.9)	5 (38.5)	0.047*
	NON RELATED	3 (23.1)	8 (61.5)	
STEM CELL SOURCE	PERIPHERAL	13 (100)	13 (100)	-
	HARVEST	0 (0)	0 (0)	
PRE-RANSPLANTATION-DISEASE REMISSION	NOT REMISSION	0 (0)	0 (0)	-
	REMISSION	13 (100)	13 (100)	
TBI USED	NO	13 (100)	13 (100)	-
	YES	0 (0)	0 (0)	
PREPARATION REGIME	MYELOABLATIF	13 (100)	13 (100)	-
	REDUCED INTENSITY	0 (0)	0 (0)	

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GVHD PROPHYLAXIS	Cyclosporine (2x1.5 mg/kg)-methotrexate (10 mg/m2)	0 (0)	0 (0)	1
	Cyclosporine (2x1.5 mg/kg)-methotrexate (10 mg/m2)- post TX cyclosporine (2 x3 mg/kg-PO	13 (100)	12 (92.3)	
	Cyclosporine (2x1.5 mg/kg)-methotrexate (10 mg/m2) – ATG-(2.5 mg/kg/day)-post TX cyclosporine (2 3 mg/kg-PO	0 (0)	1 (7.7)	
	DİĞER	0 (0)	0 (0)	
GRADE	≤2	11 (84.61)	6 (46.15)	0.097
	>2	2 (15.38)	7 (53.84)	
POST TRANSPLANT cGVHD OCCURRENCE	≤220 day	2 (15.38)	10 (76.92)	0.006*
	>220 day	11 (84.61)	3 (23.07)	
cGVHD ORGAN INVOLVEMENT	SKIN	2 (15.4)	2 (15.4)	0.075
	LIVER	5 (38.5)	1 (7.7)	
	GUT	1 (7.7)	2 (15.4)	
	LUNG	3 (23.1)	0 (0)	
	SKIN and GUT	0 (0)	2 (15.4)	
	SKIN and LıVER	2 (15.4)	6 (46.2)	
	GUT and LIVER	0 (0)	0 (0)	
	OTHERS	0 (0)	0 (0)	
ECP 1 WEEK RESPONSE	CR	0 (0)	0 (0)	0.16
	VGPR	3 (23.1)	2 (15.4)	
	PR	3 (23.1)	1 (7.7)	
	SD	6 (46.2)	4 (30.8)	
	PD	1 (7.70)	6 (46.2)	
ECP 1 MONTH RESPONSE	CR	0 (0)	0 (0)	0.03*
	VGPR	7 (53.8)[a]	2 (15.4)[b]	
	PR	3 (23.1)[a]	3 (23.1)[a]	
	SD	3 (23.1)[a]	2 (15.4)[a]	
	PD	0 (0)[a]	6 (46.2)[b]	
ECP LAST SEEN	CR	8 (61.5)[a]	0 (0)[b]	0.002*
	VGPR	3 (23.1)[a]	1 (7.7)[a]	
	PR	0 (0)[a]	2 (15.4)[a]	
	SD	0 (0)[a]	2 (15.4)[a]	
	PD	2 (15.4)[a]	8 (61.5)[b]	
ECP SIDE EFFECTS	Not Happened	13 (100)	13 (100)	-
	Happened	0 (0)	0 (0)	

*AML: Acute myelocytic leukemia, ALL: Acute lymphoblastic leukemia, CR:Complete remission, ECP: Extracorporeal photopheresis, cGVHD: Chronic graft versus host disease, MDS: Myelodysplastic syndrome, PD: Progressive disease, PO: Peri oral, PR: Partial remission, SD: Stable disease, TBI: Total body irradiation, TX: Stem cell transplant, VGPR: Very good partial remission. Different superscript letters in each row show a statistically significant difference (P ≤ .05), *Statistically significant*

Table III. *Univariate and multivariate Cox regression analyses for chronic graft versus host disease, n=26*

Variables in the Equation	Univariate		Multivariate	
	HR [95% CI]	P	HR [95% CI]	P
Age	**1.038 [0.999-1.079]**	**0.049**		
Sex [male]	0.754 [0.235-2.416]	0.63		
PRIMARY DISEASE (ALL)	0.155 [0.019-1.273]	0.082		
PRIMARY DISEASE (NON HODGKIN)	9.925 [0.854-115.352]	0.066		
PRIMERY DISEASE [MDS]	1.519 [0.307-7.513]	0.6		
PRIMARY DISEASE (OTHER)	0.69 [0.165-2.885]	0.69		
DONOR FEATURE	0.846 [0.255-2.68]	0.75		
DONOR KINSHIP	**4.927 [1.288-18.847]**	**0.019**	**15.4 [1.456-162.96]**	**0.023**
GVHD PROPHYLAXY	**11.503 [1.043-126.84]**	**0.046**		
POST TRANSPLANT GVHD OCCURRENCE >220	**0.093 [0.02-0.434]**	**0.003**	**0.076 [0.006-0.947]**	**0.045**
GVHD ORGAN INVOLVEMENT (LIVER)	0.333 [0.03-3.722]	0.37		
GVHD ORGAN INVOLVEMENT (GUT)	0.566 [0.05-6.389]	0.64		
GVHD ORGAN INVOLVEMENT (LUNG)	0 [0-0]	0.98		
GVHD ORGAN INVOLVEMENT (SKIN and GUT)	4.848 [0.623-37.707]	0.13		
GVHD ORGAN INVOLVEMENT (SKIN and LIVER)	1.715 [0.34-8.642]	0.51		
STEROID DURATION (DAYS)	0.998 [0.995-1.002]	0.45		
ECP USAGE TIME (DAYS)	1.0002 [0.995-1.005]	0.93		
CYCLE OF ECP USE	1.005 [0.925-1.093]	0.88		
STEROID DOSE DURING ECP	**1.02 [1.0007-1.041]**	**0.042**		
ECP 1 WEEK RESPONSE [VGPR]	1.113 [0.069-17.941]	0.93		
ECP 1 WEEK RESPONSE [PR]	3.112 [0.343-28.246]	0.31		
ECP 1 WEEK RESPONSE [SD]	6.996 [0.826-59.259]	0.07		
ECP 1 MONTH RESPONSE [VGPR]	6.297 [0.65-61.014]	0.11		
ECP 1MONTH RESPONSE [PR]	4.589 [0.409-51.441]	0.21		
ECP 1 MONTH RESPONSE [SD]	**16.394 [1.934-138.963]**	**0.01**	**16.36 [1.659-161.49]**	**0.016**
ECP LAST SEEN [CR]	1.118 [0.075-17.989]	0.966		
ECP LAST SEEN [VGPR]	0.178 [0.022-1.44]	0.100		
ECP LAST SEEN [PR]	0.295 [0.036-2.41]	0.255		
ECP LAST SEEN [SD]	2.64 [0.474-14.75]	0.267		
GVHD GRADE >2	**4.003 [1.227-13.053]**	**0.021**	**4.85 [1.344-17.5]**	**0.015**
APPLYING ECP AFTER GVHD (DAYS)	1 [0.996-1.003]	0.82		

HR: Hazard ratio, CI: Confidence Interval ECP: Extracorporeal Photopheresis, TBI: Total body irradiation, CR: Complete remission VGPR: Very good partial remission, SD: Stable disease, PD: Progressive disease, GVHD: graft versus host disease

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In univariate Cox regression analysis; Age, donor proximity, cGVHD prophylaxis, time to reccurrence of cGVHD after transplantation, steroid dose during ECP, ECP 1st month response and cGVHD grade had significant HR p values (Post transplant GVHD time-0.045/ ECP 1 month response-0.016/ GVHD grade-0.015). A multivariate Cox regression model was created with these parameters with significant p values. Obtained results; for cGVH, donor proximity, duration of cGVHD after transplantation, ECP 1st month response and cGVHD grade were found to be significant; HR p value <0.05 (Table III).

According to the univariate-cox regression analysis in cGVHD patients, an increase in the dose of steroid drug by one unit during ECP was found to be 1.02, and an increase in patient age by one unit increased the risk of deceased by 1.038 times. It was observed that the use of cGVHD prophylaxis (post-transplant oral cyclosporine, methotrexate, antithymocyte globulin) increased the risk of mortality 11,503 times compared to not using the prophylaxis (post-transplant oral cyclosporine, methotrexate).

According to the results of multivariate Cox regression analysis in cGVHD patients; In patients in whom the donor was unrelated, the risk of deceased was 15.4 times higher than that of being a relative. The risk of deceased was 13,157 times higher in patients with cGVHD less than 220 days after transplantation compared to patients with more than 220 days. The risk of deceased was 16.36 times higher in patients with ECP 1st month response SD compared to patients with PD. Patients with higher cGVHD grade levels (> 2) were 4.85 times more likely to die than patients with lower (≤ 2) cGVHD grade levels.

Kaplan-Meier (KM) survival analysis was performed on variables considered as binary in multivariate Cox regression analysis. Table IV shows KM results and Figures 2, 3, 4 and 5 show donor affinity, ECP 1st month response, time to occurrence of cGVHD after transplantation, and survival by grade, respectively. In CM analyzes, survival of patients with low grade (≤ 2) was significantly higher than patients with higher grade (> 2). Patients with a relative of the donor had longer survival than patients who were unrelated. Finally, patients with a longer time to cGVHD after transplantation (>220) and a lower grade (≤2) had significantly higher survival (Table IV).

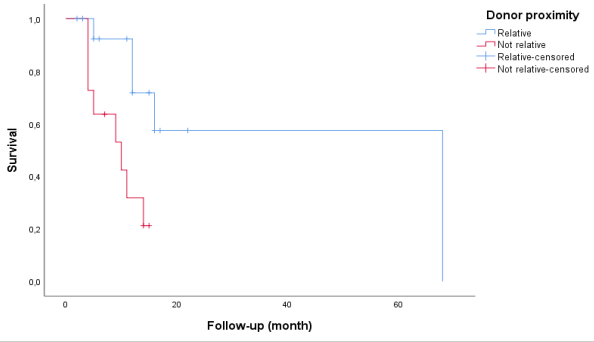

Figure 2. *Survival curve for donor proximity for chronic GVHD (p value-1)*

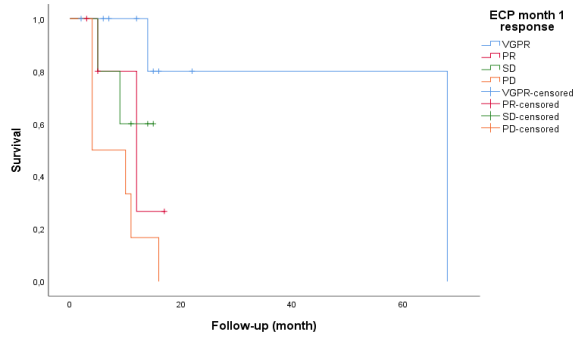

Figure 3. *Survival curve for ECP Month 1 response for chronic GVHD (p value-0.03)*

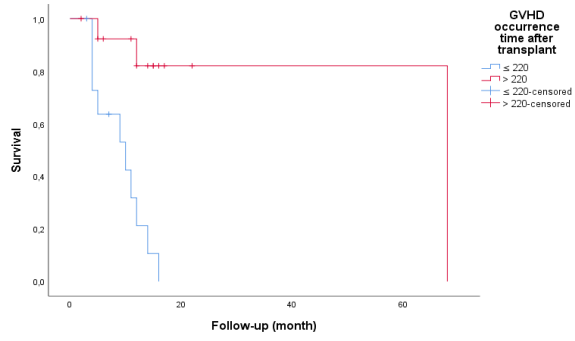

Figure 4. *Survival curve for time to cGVHD after transplantation for chronic GVHD (p value-0.097)*

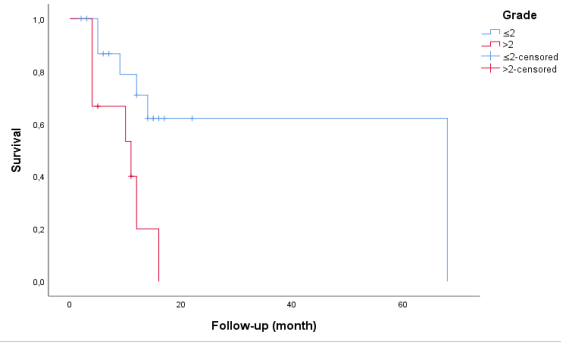

Figure 5. *Effect of the degree of chronic gvhd on survival (p value-0.006)*

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Table IV. *Survival results for variables that were significant in multivariate Cox regression for chronic graft versus host disease*

		Kaplan-Meier Analysis	
		Survival time (month)	Log-Rank
		Mean ± SE	p-value
DONOR KINSHIP	Relative	44.2 ± 10.51	0.009*
	Non Relative	9.39 ± 1.33	
ECP 1 month response	VGPR	57.2 ±13.66	0.007*
	PR	11.93 ± 1.89	
	SD	11.8 ± 1.84	
	PD	8.16 ± 2.03	
GVHD OCCURRENCE AFTER TRANSPLANTATION (≤ 220 DAYS)		9.18 ± 1.35	<0.001*
GVHD OCCURRENCE AFTER TRANSPLANTATION (>220 DAYS)		57.41 ± 8.39	
Grade ≤ 2		45.75 ± 8.71	0.012*
Grade > 2		9.73 ± 7.33	

*ECP: Extracorporeal photopheresis, GVHD: Graft versus host disease, Min-Max: Minimum-Maximum, VGPR: Very good partial response PR:Partial response, SD:Stable disease, PD: Progressive disease. *Statistical significance*

4. DISCUSSION

Our findings show statistically significant differences in cGVHD in terms of donor proximity, time to onset of cGVHD post-transplant, ECP 1st month response and the last follow-up of the patient after ECP and the degree of involvement that affected survival in cGVHD. The survival rate of cGVHD patients with grade 2 and higher involvement was significantly reduced. It was determined that the time to diagnosis of cGVHD after stem cell transplantation affected survival, and especially if the cGVHD developed after 220 days post-transplant, the rate of survival was high.

Many parameters are effective in the development of cGVHD in allogeneic stem cell transplantation. cGVHD treatment strategies are based on previous studies. Some of these studies are focused on transplantation parameters and ECP. ECP stands out as a treatment option that can be easily applied to patients and does not suppress the patient's immune system. In cGVHD, ECP provides effective treatment by causing changes in the function of immune T cells [13,14].

In the study of Sakellari and his colleagues, they reported that ECP must be performed before irreversible systemic damage occurs. Its use in the first phases of cGVHD was found to be more effective. Patients included in this study were those with steroid-refractory cGVHD but without irreversible systemic damage [15].

In the guideline updated by the American Apheresis Committee in 2023, ECP application in both acute and chronic GVHD was evaluated as category 2b. For cGVHD, a course is typically once or twice a week for up to 3 months or until disease stabilization, then tapered to a single course every 2 to 4 weeks (evaluated at 2 – to 3-month intervals) [16].

In this study, the use of ECP in cGVHD patients was more effective, especially in patients with GVHD that developed 220 days after transplantation and in patients with grade 2 and above. ECP application was applied to the patients for at least 4 sessions per week.

The consensus recommendation in the review by Drexler et al., stated that treatment should be administered 2 consecutive days per week or every 2 weeks for at least 8-12 weeks or until a noticeable response was achieved. ECP applications have been shown to be effective, with overall response rates of 57% for aGvHD and 38% for cGvHD [13].

In this study, in patients who developed cGVHD, in a year, overall survival rate was 56.6%, and in two years overall survival rate was 47.6%. ECP use in cGVHD affected the survival response at 1 month, 57.2 % for VGPR, 11.93 % for PR, 11.8 % for SD, and 8.16 % for PD. It was observed that the survival of patients who developed cGVHD after 220 days, was positively affected (57.41 months). Patients with grade 2 and above cGVHD, were adversely affected (9.73 months). NIH consensus criteria were used in the evaluation of patients [12].

In a multicenter study of Dal et al., advanced cGvHD was detected in two-thirds of the patients. Many organs were affected in 50% of the patients. The mean response rate in cGVHD was 46.5%. The overall survival was calculated as 41% at the end of the mean 1-year follow-up of the patients. The rate of mortality due to any reason was observed as 59% in the follow-ups of the patients after stem cell transplantation. It was observed that the overall survival was remarkably high in patients in whom ECP was successful [17].

In the analysis of this study, the mean survival time in patients was approximately 32 months. The 1-year survival rate was approximately 53%, and 2-year survival rate was approximately 47%. The patients who underwent ECP due to cGVHD were given steroids in parallel with the current treatment, and a one unit increase in the steroid dose, increased the risk of mortality by 1.02 times, and an increase in the patient's age by one year increased the risk of mortality 1.038 times. Similarly, patients taking cGVHD prophylaxis (post-transplant oral cyclosporine, methotrexate, antithymocyteglobulin) had a 11.503-fold increased risk of mortality compared to patients receiving cGVHD prophylaxis (post-transplant oral cyclosporine methotrexate). In patients in whom the donor was unrelated, the risk of mortality was 15.4 times higher than the patients with a related donor transplant. The risk of mortality was 13,157 times higher in patients who developed cGVHD in less than 220 days after transplantation when compared to patients who developed cGVHD after 220 days. Patients with ECP 1 month response SD had a 16.36-fold increased risk of mortality compared to patients with PD. Finally, patients with higher cGVHD grade levels (> 2) were 4.85 times more likely to die than patients with lower cGVHD grade levels (≤ 2).

In a review article by Canto et al., ECP application was shown as category 2 level 1b, with an emphasis on the ASFA 2016 guide. They reported a median overall response rate of 75% for cGVHD (median, 76%; IQR, 66% to 84%) in their case series.

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Reducing steroid doses could be achieved without any difference in cGVHD (median, 70%; IQR, 55% to 81%). It is argued that there is consensus regarding the safety and excellent tolerability of ECP [18].

The overall survival rate in our study was 53.6% for the 1st year and 47.6% for the 2nd year. In the response evaluation of ECP use after one month, survival rate was found to be 5.2% in patients with VGPR. Survival was found to be better in patients who developed cGVHD 220 days after transplantation. There was no difference between genders. ECP application was safely applied and no side effects occurred.

Limitation

In case there was no pathological diagnosis, the diagnosis of cGVHD after transplantation was decided according to the patient's post-transplant GVHD development time. GVHD that developed after 100 days was considered chronic. In the evaluation of the response of the patients, patients who could not be fully determined on the scale whether they were grade 1 or 2, were considered to have lower grades.

Conclusion

In steroid-refractory patients who developed cGVHD after allogeneic stem cell transplantation, steroid use during ECP, the type of prophylaxis used for cGVHD in stem cell transplantation, donor kinship, the development time of cGVHD after transplantation (especially in patients who developed cGVHD after 220 days), and the degree of cGVHD disease affected survival.

Compliance with Ethical Standards

Ethics committee approval: The study was approved by the Non-interventional Clinical Research Ethics Committee of Inonu University, (date: 26.04.2022, approval number 2022/3326). The study was conducted in accordance with the Declaration of Helsinki.

Conflict of Interest: No conflict of interest was declared by the authors. **Financial Support:** The authors declared that they received no financial support.

Authors contributions: AK: Conducting the study and writing the article, MAE: Supervising, IK, EK: Collection of the data, IB, SB and SA: Writing the article, FHY: Providing biostatistical support for the study. All authors approved the final version of the article.

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Long-term follow-up of infective endocarditis: Rates of reinfection, mortality, and predictors of outcome

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ABSTRACT

Objective: Infective endocarditis (IE) is a severe condition characterized by high mortality rates. We aimed to assess reinfection and mortality rates in IE patients at a tertiary referral center during long-term follow-up.

Patients and Methods: We retrospectively analyzed 204 patients meeting modified Duke criteria for definite IE between 2009 and 2019. Early reinfection was defined as occurrence within 6 months, and late reinfection was defined as occurrence 6 months after the initial diagnosis.

Results: Mean follow-up duration was 40.3 ± 26.4 months. Valve surgery was performed in 125 patients (69.8%), while 54 (30.2%) received medical therapy alone. Early reinfection was
seen in 9 patients (5.1%), and late reinfection in 12 patients (6.7%). Staphylococci (41.9%), Streptococci (26.3%), and Enterococci (15.6%) were common pathogens. Peripheral limb emboli predicted reinfection (HR 4.118, 95% CI 1.471-11.528, p=0.007). Survival rates at 1, 2, and 5 years were 70.2%, 65.7%, and 57.3%, respectively. Age (HR 1.030, 95% CI 1.011 – 1.049, p=0.002), peripheral limb emboli (HR 2.994, 95% CI 1.509-5.940, p=0.002), and septic shock (HR 2.357, 95% CI 1.097-5.065, p=0.028) predicted mortality.

Conclusion: Infective endocarditis mortality rates remain high regardless of reinfection. Peripheral limb emboli independently determine reinfection and mortality. Careful management of this group may reduce morbidity and mortality.

Keywords: Infective endocarditis, Reinfection, Long-term mortality

1. INTRODUCTION

Infective endocarditis (IE) is a destructive condition typically triggered by bacterial infections, indicating an infection of the endocardial lining of the heart or foreign materials within the heart [1]. Despite its relative rarity, the estimated annual incidence of the disease ranges from 1.5 to 11.6 cases per 100,000 individuals [2]. While a decrease in IE incidence is expected with advancements in medical diagnosis and treatment, factors such as an aging population, increased use of intracardiac devices, prosthetic valves, intravenous (IV) injections, hemodialysis, and an increase in immunosuppressed patients contribute to its rise [3].

Despite advanced diagnostic and treatment methods, in-hospital mortality remains at 25%, with 1-year mortality rates at approximately 30% and 5-year mortality rates hovering around 45%, indicating a prognosis worse than many cancer types [4,5]. Prolonged IV antimicrobial treatment, the need for frequent valve surgeries, an extended hospital stay due to serious complications (e.g., cerebrovascular), and admission to the intensive care unit impose a significant financial burden on society [6]. Additionally, among IE patients who survive the initial episode, a noteworthy complication, recurrent IE, can occur in 2% to 31% of cases [7].

The 1-year mortality of patients experiencing recurrent IE is higher than that of those with a single IE episode, further increasing the financial burden due to repeated hospitalizations and additional treatment needs [8]. These striking figures underscore the significance of long-term outcomes in IE. In this context, our study aims to determine the long-term mortality risk among patients diagnosed with IE using modified Duke criteria [9], presenting at a tertiary referral center in Turkiye.

We intend to achieve this by examining the demographic characteristics, disease features, treatment strategies, and complications of these patients, ultimately contributing to more effective patient management in clinical practice. Additionally,

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we will present the findings of the investigation exploring factors influencing early and late reinfection, as well as long-term mortality in patients, and their impact on clinical outcomes.

2. PATIENTS and METHODS

Study Population

Between 2009 and 2019, a total of 204 consecutive adult patients with a definitive diagnosis of IE were retrospectively included in our tertiary care hospital. Inclusion criteria were defined as follows: 1) adult patients aged 18 years and older, and 2) patients with a definite diagnosis of IE according to modified Duke criteria. Eleven patients with incomplete data were excluded from the study, and an additional 15 patients could not be reached during follow-up, leaving 178 patients for evaluation. The diagnosis of IE in all suspected cases was confirmed by a multidisciplinary endocarditis team consisting of cardiologists, infectious disease specialists, and cardiovascular surgeons. The study protocol was approved by the Ethics and Research Committee of our hospital on 13.03.2024 with the Ethics Committee Decision numbered 2024.01-12 and complies with the principles in the Declaration of Helsinki.

Data Collection and Follow-up

All data relied on a systematic retrospective review of electronic medical records encompassing all patient documents, echocardiography, and laboratory results. Given that all patient records were linked to the national death reporting system, deaths occurring outside the hospital were also included. All patients were treated in accordance with predefined surgical indications and treatment algorithms outlined by the American Heart Association and the European Society of Cardiology [10,11]. Microbiological diagnosis was established through blood cultures (three sets of blood cultures taken half an hour apart), extracted material, or valve cultures. Before concluding negative blood culture endocarditis (BCNE), specific analyses including serological tests for more specific pathogens such as Bartonella, Mycoplasma, Brucella spp., and Chlamydia spp., etc., were conducted using enriched culture media. Transthoracic (TTE) and transesophageal (TEE) echocardiography were performed according to European guidelines for patients with clinical or microbiological suspicion of IE and for diagnosing intracardiac complications [12]. Evaluation using PET/CT was conducted when paravalvular extension, systemic, and cerebrovascular embolism could not be determined by CT and Duke criteria. The primary outcome of the study was all-cause mortality, while the secondary outcome was the occurrence of any early or late reinfection.

Definitions

Early reinfection was defined as recurrence of IE with the same pathogen (equals relapse) or a new episode caused by a different microorganism within 6 months after the index event. Late reinfection was defined as recurrence of IE with the same pathogen or a new episode caused by a different microorganism occurring 6 months after the index event [13]. Stroke was characterized by clinical and radiographic abnormalities consistent with acute stroke, encompassing both clinical presentations during treatment and stroke related to surgery. Peripheral embolization, excluding stroke, was defined as clinical and nuclear/radiographic abnormalities consistent with embolization. Diabetes Mellitus (DM) was defined as having at least two fasting plasma glucose levels ≥ 126 mg/dL or plasma glucose levels ≥ 200 mg/dL after meals or the use of antidiabetic drugs. Hypertension was defined as systolic blood pressure >;140 mmHg and/or diastolic blood pressure >;90 mmHg or current use of antihypertensive drugs by the patient. Heart failure was defined as a presentation including at least two of the following: NYHA class III-IV, acute decompensation on chest X-ray or echocardiogram, new peripheral edema.

Statistical Analysis

The normality of variables was evaluated utilizing Kolmogorov-Smirnov tests, histograms, and probability plots. Numeric variables are reported as mean ± standard deviation or median (interquartile range) depending on their distribution. Categorical variables are expressed as percentages (%). Numerical variables between two groups were compared using either Student's t-test or Mann-Whitney U test, while categorical variables were compared using Chi-square or Fisher's exact test. Kaplan-Meier modeling was utilized to depict the duration until the cessation of service events, serving as a proxy for mortality following aneurysm surgery. This analysis was conducted using SPSS 26.0 software (SPSS,Chicago, IL). Statistical comparisons of the time-to-event data for various interventions and controls were performed using log-rank tests and reported as median survival rates (years ± 95% CI). Additionally, all patients, a single-variable Cox proportional hazards model was utilized to compute hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) for long-term mortality. Multivariable Cox proportional models were employed to assess potential independent predictors for survival. The significance level was set at $p < 0.050$.

3. RESULT

A total of 178 patients with a mean age of 54.9 ± 15.4 years were included in the study, of which 63 (35.4%) were female. The patients were followed for an average of 40.3 ± 26.4 months. The baseline characteristics of the patients are detailed in Table 1. Reinfection occurred in a total of 21 (11.8%) patients, with 9 (5.1%) classified as early reinfection and 12 (6.7%) as late reinfection. While the characteristic features and comorbidities of the study group were similar in terms of reinfection, hemodialysis (p=0.003), and peripheral emboli (p = 0.006) were found to be higher in the group experiencing early and late reinfections. The most common infectious agents consisted of streptococci in 26.3% (47/178), Staphylococcus in 22.3% (40/178), and Enterococcus in 15.6% (28/178) of cases. Left-sided valve involvement was present in the majority of patients (90.5%). Isolated pacemaker lead endocarditis was observed in 21 (11.8%) patients, pulmonary valve endocarditis in 1 (0.6%) patient, and tricuspid valve endocarditis in 7 (3.9%) patients. Endocarditis related to substance abuse was identified in 5 (2.8%) patients. Congenital heart disease was present in 8 (4.5%) patients, with 1 being cyanotic and 7 non-cyanotic. Medical treatment along with surgery was administered to 69.8% of the patients.

Table I. *Characteristics and Comorbidities of the Study Group in terms of Reinfection*

	All patients	No reinfection	Early reinfection	Late reinfection	P Value
n (%)	**178 (100%)**	**157 (88.2%)**	**9 (5.1%)**	**12 (6.7%)**	
Age	54.9 ± 15.4	54.5 ± 15.5	58.7 ± 10.4	54.6 ± 16.1	0.750
Female (n, %)	63 (35.4%)	54 (34.4%)	4 (44.4%)	5 (41.7%)	0.742
DM (n, %)	29 (16.3%)	28 (17.8)	1 (11.1%)	0 (0%)	0.248
Hemodialysis (n, %)	9 (5.1%)	5 (3.2%)	1 (11.1%)	3 (25%)	0.003
LVEF (%)	53.7 ± 10.5	54.3 ± 10.7	46.1 ± 6	51.7 ±8.9	0.320
Immunosuppressive Treatment (n, %)	2 (1.1%)	2 (1.3%)	0 (0%)	0 (0%)	0.873
Stroke (n, %)					0.495
Ischemic stroke	13 (7.3%)	12 (7.6%)	1 (11.1%)	0 (0%)	
Hemorrhagic stroke	6 (3.4%)	5 (3.2%)	1 (11.1%)	0 (0)	
Septic Pulmonary Emboli (n, %)	18 (10.7%)	16 (10.9%)	2 (22%)	0 (0%)	0.260
Splenic and/or Renal Emboli (n, %)	12 (6,7%)	11 (7%)	0 (0%)	1 (8.3%)	0.699
Peripheral Limb Emboli (n, %)	14 (7.9%)	9 (5.7%)	3 (33.3%)	2 (16.7%)	0.006
Abscess (n, %)	21 (12.5%)	20 (13.6)	1 (11.1%)	0 (0%)	0.388
Treatment					0.596
Medical (n, %)	54 (30.2)	47 (29.7%)	2 (22.2%)	7 (77.8%)	
Surgical (n, %)	125 (69.8%)	111 (70.3)	5 (41.7%)	7 (58.3%)	
Substance Abuse (n, %)	5 (2.8%)	4 (2.5%)	0 (0%)	1 (8.3%)	0.440
Congenital Heart Disease (n, %)	8 (4.5%)	7 (4.4%)	1 (11.1%)	0 (0%)	0.474
Prosthetic valve endocarditis (n, %)	61(34.3 %)	54(34.4 %)	4(44.4 %)	3(25 %)	0.646
Causative Agents(n, %)					0.136
Streptococci	47 (26.3%)	43 (27.4%)	2 (22.2%)	2 (16.7%)	
MSSA	28 (15.6%)	22 (14%)	1 (11.1%)	5 (41.7%)	
MRSA	12 (6.7%)	10 (6.4%)	2(22.2%)	0 (0%)	
Enteroccoci	28 (15.6%)	25 (15.9%)	1 (11.1%)	2 (16.7%)	
BCNE	17 (9.5%)	17 (10.8%)	0 (0%)	0 (0%)	
CoNS	35 (19.6%)	31 (19.8%)	1 (11.1%)	3 (25%)	
Other	8 (4.5%)	7 (4.5%)	1 (11.1%)	0 (0%)	
Candida-Aspergillus	3 (1.7%)	2 (1.3%)	1 (11.1%)	0 (0%)	
Valve Involved (n,%) Mitral					0.508
	72 (40.4%)	64 (40.8%)	4 (44.4%)	4 (33.3%)	
Aortic	54 (30.3%)	49 (31.2%)	2 (22.2%)	3 (25%)	
Mitral + aortic	17 (9.6%)	16 (10.2%)	0 (0%)	1 (8.3%)	
Trikuspid	7 (3.9%)	5 (3.2%)	0 (0%)	2 (16.7%)	
Pacemaker	21 (11.8%)	16 (10.2%)	3 (33%)	2 (16.7%)	
Pulmonary	1 (0.6%)	1 (0.6%)	0 (0%)	0 (0%)	

BCNE: Blood culture-negative endocarditis, CoNS: Coagulase-negative Staphylococci, DM: diabetes mellitus, MSSA: methicillin-sensitive Staphylococcus aureu, MRSA: Methicillin-resistant Staphylococcus aureus, LVEF: Left ventricle ejection fraction

Table II. *Univariate and multivariate Cox regression analysis for endpoints. First reinfection (early and late reinfections combined)*

	Univariate analysis		Multivariate analysis	
	Hazard ratio 95%CI (lower-upper)	P value	Hazard ratio 95%CI (lower-upper)	P value
Age	1.007 (0.979-1.036)	0.620		
Gender	1.402 (0.591-3.327)	0.444		
DM	2.643 (1.095-6.379)	0.031	1.881 (0.750-4.715)	0.178
Hemodialysis	2.060 (0.946-4.487)	0.069		
LVEF	0.967 (0.936-0.999)	0.040	0.969 (0.936-1.003)	0.076
Peripheral Limb Emboli	14.949 (4.595-48.635)	<0.001	4.118 (1.471-11.528)	0.007
Surgical treatment	0.788 (0.316-1.970)	0.611		
Staphylococcal infection	1.224 (0.516-2.906)	0.646		

DM: diabetes mellitus, LVEF: Left ventricle ejection fraction

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Table III. *Univariate and multivariate Cox regression analysis for All-cause mortality.*

	Univariate analysis		Multivariate analysis	
	Hazard ratio 95%CI (lower-upper)	P value	Hazard ratio 95%CI (lower-upper)	P value
Age	1.036 (1.019-1.054)	**<0.001**	1.030 (1.011-1.049)	**0.002**
Gender	1.308 (0.824-2.077)	0.254		
DM	1.282 (0.717-2.293)	0.401		
HT	1.537 (0.965-2.448)	0.070		
Stroke	0.843 (0.366-1.941)	0.688		
Hemodialysis	2.345 (1.076-5.109)	**0.032**	1.086 (0.443-2.658)	0.857
LVEF	0.967 (0.936-0.999)	**0.040**	0.993 (0.973-1.013)	0.504
Peripheral limb emboli	2.711 (1.422-5.169)	**0.002**	2.994 (1.509-5.940)	**0.002**
Re-endocarditis	1.706 (0.938-3.105)	0.080		
Septic shock	3.268 (1.663-6.422)	**0.001**	2.357(1.097-5.065)	**0.028**
Surgical treatment	0.461 (0.292-0.727)	**0.001**	0.644 (0.391-1.062)	0.085
Staphylococcal infection	1.521 (0.962-2.406)	0.073		

DM: diabetes mellitus,HT: Hypertension, LVEF: Left ventricle ejection fraction

When comparing patients with prosthetic valve endocarditis (PVE) and native valve endocarditis (NVE) in the index case, there was no significant difference in terms of reinfection incidence (p=0.530). There was no significant difference in the risk of early and late reinfection based on the microorganisms causing the index case. Any first re-infection, early, and late reinfection patients were combined for analysis. Univariate Cox regression analyses were conducted with all parameters to identify determinants of the first reinfection. Parameters such as DM (p=0.031), LVEF (p=0.040), and Peripheral emboli (p<0.001) were presented in Table II, showing a significant association with the first reinfection. In the multivariate Cox regression analysis with these parameters, Peripheral emboli (p=0.007) were identified as independent determinants for reinfection.

The in-hospital mortality rate was 18%, and the mortality rates at 1 year, 2 years, and 5 years were determined as 29.8%, 34.3%, and 42.7%, respectively. Among the 178 patients, 124 (69.7%) underwent surgical treatment, while 54 (30.3%) received only medical treatment. Univariate Cox regression analyses were conducted with all parameters to identify determinants of long-term mortality. Parameters such as Age (p<0.001), hemodialysis (p=0.032), LVEF (p=0.040), peripheral emboli (p=0.002), septic shock (p=0.001), and non-surgical treatment (p=0.001) were presented in Table III, showing a significant association with long-term mortality. In the multivariate Cox regression analysis with these parameters, Age (p=0.002), peripheral emboli (p=0.002), and septic shock (p=0.028) emerged as independent determinants of long-term mortality.

The Kaplan-Meier survival analysis indicated a significant increase in long-term mortality in patients with early reinfection and those treated solely with medical therapy (Log-rank: p=0.016, p<0.001). However, no significant difference was observed in terms of causative agents (Log-rank: p=0.082) (Figure 1).

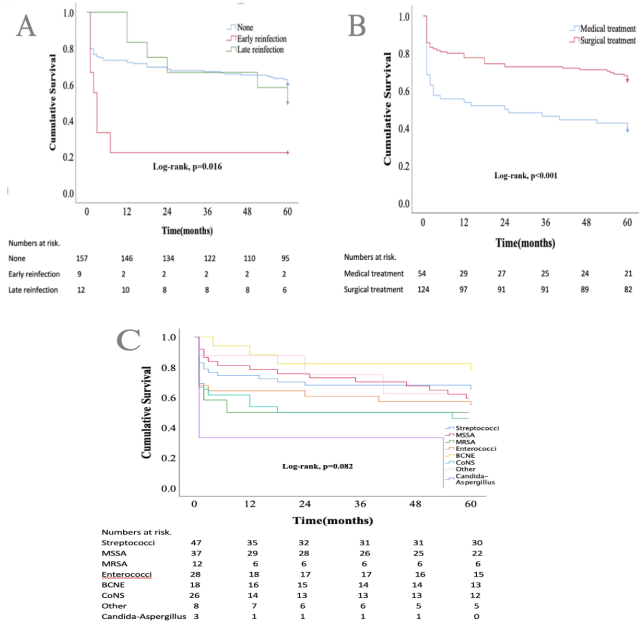

Figure 1. *Kaplan–Meier survival curves for Reinfection status in IE patient (A), medical and surgical treatment status (B), and causative agents (C).*

4. DISCUSSION

We report the outcomes of a retrospective cohort study evaluating the clinical characteristics and outcomes of adult patients diagnosed with IE treated at our tertiary cardiovascular center. The average follow-up duration for our study was 40.3 ± 26.4 months.

The main findings of our study are summarized below:

1. Reinfection occurred in a total of 21 patients (11.8%), with 9 cases (5.1%) classified as early reinfection and 12 cases (6.7%) as late reinfection.

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2. Peripheral emboli (p=0.007) were identified as independent determinants in the recurrence of infection.
3. In-hospital mortality was 18%, and mortality rates were determined to be 29.8% at 1 year, 34.3% at 2 years, and 42.7% at 5 years.
4. Age (p=0.002), peripheral emboli (p=0.002), and septic shock (p=0.028) emerged as independent predictors of long-term mortality.

The rates of early and late reinfection observed in our study were comparable to existing literature. We observed an incidence of 5.1% for early reinfection and 6.7% for late reinfection. The rate of early reinfection leading to prosthetic valve dysfunction was found to be 4%. Our findings align with recent studies suggesting an incidence range of 4% to 12% [14].

There is controversial data and conclusions in between studies in literature about re-infection of IE. In a study conducted by Heiro et al., IV drug use, DM and hemodialysis were identified as significant risk factors for recurrent episodes of IE [15]. In another study, theyconcluded that IV drug usage, prosthetic valve endocarditis and infection caused by S. Aureus were associated with re-infection [16]. Moreover, a study conducted by Thornhill et al., heart failure at presentation and the presence of a pacemaker were independent predictors [17]. In our study, only independent determinants of any reinfection were identified as peripheral emboli during the index case. In our cohort, statistically significant risk factors for reinfection did not include prosthetic valve, the type of pathogen causing IE, age, surgical treatment, and hemodialysis. Furthermore, in our study, DM and reduced LVEF during the index case were identified as risk factors for reinfection in univariate analysis, but they did not reach statistical significance in multivariate analysis.

Hemodialysis is a well-known factor associated with both recurrent infections and mortality. The presence of catheter-related bacteremia in recurrent IE and hemodialysis is not surprising. Studies have shown that healthcare-associated IE represents nearly one-third of all cases, and catheters are a significant source of infection in these patients [18]. In our study, hemodialysis was observed in 25% of late reinfections, but it was not identified as an independent variable in Cox regression analysis. This is likely due to the inadequacy of our sample size. Similarly, certain variables related to reinfection, such as intravenous drug dependence and Staphylococcus aureus, which have been observed in other studies [19,20], may not have been detected in our study due to the limited number of patients.

Despite all the advancements in diagnosis and treatment, IE continues to be a fatal disease in the long term. In our study, the mortality rates at 1, 2, and 5 years of follow-up were 29.8%, 34.3%, and 42.7%, respectively. Independent determinants of mortality were identified as age, peripheral limb emboli, and septic shock in multivariate Cox regression analysis.

Peripheral emboli have been found to be an independent predictor of both reinfection and IE mortality. In the study by Tahon et al., peripheral emboli were identified as an independent predictor of reinfection [13]. In the study by Jose Fabri et al., the frequency of symptomatic peripheral emboli was found to be 21.1% [21], and hospital mortality was significantly higher in patients with symptomatic peripheral emboli at the time of diagnosis. Additionally, in a recent study, consistent with our findings, age and peripheral embolic phenomena have been defined as an independent determinant of mortality [22].

Septic shock, independently of IE, is associated with high morbidity and mortality. In many studies conducted on patients with IE who meet the criteria for septic shock and have bacteremia, a significantly higher mortality has been observed [23,24]. In our study, both univariate and multivariate Cox regression analyses identified septic shock as an independent predictor of mortality (p=0.010).

Along with increasing age, patients tend to have more comorbidities, chronic illnesses, and increased susceptibility to infections. Similar to many other diseases, advanced age also contributes to mortality in IE. In our cohort, mortality significantly increased with age and was statistically significant. Our findings are in line with numerous studies in the literature [5,24,25].

In a study conducted using data from electronic databases in five different countries, it was observed that mortality associated with Staphylococcus infections in native valve IE was more pronounced [26]. Staphylococcal infections were linked to a higher mortality rate due to more frequent abscess formation, complete valve damage, and increased complication rates. In one study, the in-hospital mortality for Staphylococcus IE was reported as 45% [27]. Although our study showed a borderline significance in mortality when comparing Staphylococcal infections with other pathogens, no statistically significant difference was found (p=0.073).

The overall in-hospital mortality in our cohort was 18% (32/178). This rate was similar to the mortality reported in a study by Castillo and colleagues (21%) [28]. Patient characteristics, complications during the index case, and treatments administered lead to varying in-hospital mortality rates in different studies. In a study by Cebelli et al. [29], in-hospital mortality ranged from 15% to 25%, with a one-year mortality rate of 40%. In a study by Botelho and colleagues, a one-year mortality rate of 8.2% was reported [30]. Both of these studies are similar findings when compared to ours in terms of mortality rates.

Many contemporary studies have identified valve surgery in IE as a favorable prognostic factor [31]. In our study, although valve surgery was identified as an independent determinant of mortality and a good prognostic indicator in univariate Cox regression analysis, it did not reach statistical significance in multivariate analysis. We believe this difference may be attributed to our center being predominantly a referral center for patients requiring high-risk surgery. These variations likely stem from the complex pathology and clinical features of patients treated at our referral center, which accepts patients from various regions.

5. Conclusion

This study was conducted to understand the re-infection and mortality profiles of patients with IE treated at our tertiary

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cardiovascular center. Our findings indicate that early and late re-infection rates are consistent with similar studies in the literature, and peripheral emboli with septic shock are significant factors determining long – term mortality. This study may contribute to the development of strategies in IE treatment and optimization of in-hospital interventions.

Limitations

The primary limitation of our study is its retrospective cohort design and being single-centered. Acceptance of patients from all regions of the country at our center may result in higher mortality rates due to complex, complicated, and high-risk cases. Additionally, since out-of-hospital mortality causes could not be determined, mortality rates are provided as all-cause mortality rates.

Compliance with Ethical Standards

Ethics committee approval: The study was approved by the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Research Ethics Committee on 13.03.2024 with the approval number 2024.01-12. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Conflict of interest: The authors declare that they have no potential conflict of interest regarding the investigation, authorship, and/or publication of this article.

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Outcome of Ewing sarcoma in children: Twenty years experience from a single center

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ABSTRACT

Objective: Ewing sarcoma (ES) is a significant malignancy in pediatric patients, with a notable impact on bone health. Despite advances in treatment, ES still poses challenges, particularly in cases of metastasis or relapse. This study aims to evaluate the outcomes of ES in children treated at our center over a twenty-year period.

Patients and Methods: We retrospectively reviewed pediatric patients diagnosed with ES at our center between January 2004 and February 2024. Data including demographic information, tumor characteristics, treatment modalities, and survival outcomes were analyzed.

Results: Among 986 pediatric solid tumor cases, 137 (13.8%) were diagnosed with ES. After excluding ineligible cases, 115 ES cases were included in the study. The most common sites of involvement were the lower extremities. Metastatic disease was observed in 35.8% of cases, with the lungs being the most common site. Advanced age, and pelvic involvement were associated with poor prognosis. Histopathological response to neoadjuvant chemotherapy, represented by tumor necrosis rate, metastatic and relapse disease significantly influenced survival outcomes.

Conclusion: Despite multimodal therapies, ES in children, especially with metastatic disease or relapse, presents a challenging prognosis. Early diagnosis and the development of novel treatment strategies are imperative to improve outcomes for these patients.

Keywords: Ewing sarcoma, Children, Survival, Prognosis

1. INTRODUCTION

Ewing sarcoma (ES) is the second most common primary bone malignancy in pediatric patients, comprising less than 5% of all childhood cancers, with the most commonly affected bones being the femur and pelvic bones [1-4]. While, it is most commonly seen in the adolescent and pre-adolescent periods, the peak age is fifteen [5,6]. Typically, these tumors occur in bone, but sometimes they can originate in soft tissue. Soft tissue tumors constitute approximately 20% of all cases and are less frequently observed [7]. These tumors are aggressive, and treatment involves multidrug chemotherapy, radiotherapy, and surgery. With this multidisciplinary therapy, overall survival has significantly increased. The 5-year survival rate for localized ES is about 70-75% [1-3].

At the time of diagnosis, distant metastases can be detected in 25% of cases, which is a poor prognostic factor. The lungs are the most common site of metastasis. Event-free survival (EFS) rates in isolated lung metastases are around 40%, while in combined metastases, this rate drops to the 15% range [8]. Other factors affecting prognosis include histopathological response to induction therapy, primary tumor localization, the age of the patient, and the volume of the primary tumor [9].

The recurrence rate is approximately 30-40% in patients with ES [10]. The recurrence rate is higher for patients who have metastases at presentation [10]. The 5-year survival rate is less than 15% in patients with relapse [11-13]. The aim of this study was to determine the outcomes of ES in pediatric patients who were treated at our center.

2. PATIENTS and METHODS

Patients diagnosed with ES and treated at our center between January 2004 and February 2024, were retrospectively evaluated.

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Apart from demographic data, factors such as tumor localization, origin, presence of metastasis at diagnosis, surgical treatment, necrosis rate in the excised tumor, radiotherapy, presence of relapse disease, current status, and last follow-up dates were assessed to analyze patient survival and factors influencing survival. The time interval from diagnosis to death or last follow-up for surviving patients were used for overall survival (OS) analysis, while the time from diagnosis to relapse of disease in patients who achieved complete remission, progression, or death was used for event-free survival (EFS) analysis. Diagnosis of ES at our center is based on clinical, radiological, and histopathological findings. All patients underwent metastasis assessment including local magnetic resonance imaging (MRI), thoracic computed tomography (CT), bone scintigraphy, and in some cases, positron emission tomography (PET)-CT, bone marrow aspiration, and biopsy. Based on evaluation results, patients with only local disease are categorized as having localized disease (LD), while those with distant metastases are classified as having metastatic disease (MD). All patients received the same chemotherapy protocol. According to the protocol of American Intergroup POG-CCG Ewing's trial (POG-9354/CCG-7942), the patients received alternating IE (ifosfamide 1800mg/m^2/d and etoposide 100 mg/m^2/d for 5 days), and VDC/VAC (vincristine 2 mg/m^2/d, day 1, doxorubicin 75 mg/m^2/d, day 1, cyclophosphamide 1200 mg/m^2/d, day 1) therapies for 48 weeks [14]. Following three cycles of neoadjuvant chemotherapy, surgery was performed for the patients. Radiotherapy was administered to patients with more than 10% viable cells or positive surgical margins detected during pathological examinations

All cases under 18 years of age who received treatment at our center and continued regular follow-ups were included in the study. Cases who did not continue regular follow-up, received treatment at a different center, or did not consent to participate were excluded from the study. Ethical approval was obtained from the Marmara University School of Medicine Non-interventional Clinical Research Ethics Committee (approval number: 09.2024.377). Consent for study participation was obtained from all patients or their guardians.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Standard Concurrent User V 29 (IBM Corp., Armonk, New York, USA) statistical package program. Socio-demographic characteristics were compared for progression-free and overall survivals using the Log-rank test. Factors influencing progression-free and overall survivals were evaluated with univariate Cox regression analysis and Kaplan Meier analysis. The backward Wald elimination method was used in multivariate Cox regression analysis to reach the result model. A p-value <0.05 was considered statistically.

3. RESULTS

During a twenty-year period, among 986 pediatric patients diagnosed and treated for solid tumors in our pediatric oncology clinic, 137 (13.8%) were diagnosed with Ewing sarcoma (ES). Three of these cases declined to participate in the study, seven received treatment at different centers, and twelve did not attend regular follow-ups, thus they were excluded from the study. The remaining 115 pediatric cases diagnosed with ES were evaluated retrospectively. The demographic data of the cases are summarized in Table I.

Table I. *Characteristics of the patients (n=115)*

Gender	n (%)
Female/ Male	52 (45%) / 63 (55%)
Median age (years)	10.6 (range 1-17)
Primary tumor location	
Lower extremity	32 (27.8%)
Femur	21(18.2%)
Tibia	7 (6%)
Fibula	4 (3.4%)
Soft tissue	20 (17.4%)
Extremity	7 (6.0%)
Trunk	6 (5.2%)
Head and neck	5 (4.3%)
Finger	1 (0.8%)
Intraabdominal	1 (0.8%)
Upper extremity	15 (13%)
Humerıs	11(9.5%)
Scapula	4 (3.4%)
Pelvis	14 (12.1%)
Costa	19 (16.5%)
Other	15 (13%)
Metastatic at Initial Diagnosis	42 (36.5%)
Isolated Lung	18 (15.6%)
Isolated Bone	10 (8.7%)
Others	14 (12.1%)
Necrosis Rate	
More than %90	27 (23.4%)
Less than %90	38 (33%)
Undetermined	50 (43.4%)
Local treatment	112 (97.3%)
Surgery	46 (40%)
Surgery followed by radiotherapy	3 (2.6%)
Just radiotherapy	
Relapse	
Patients with relapse	30 (26%)
Patients without relapse	85 (74%)
Median Relapse Time (months)	20
Relapse Location	
Isolated Lung	13 (11.3%)
Isolated Local	6 (5.2%)
Distant Bone Relapse	11 (9.5%)
Outcome	
Complete Remission	58 (50.4%)
Exitus	50 (43.4%)
Living with Disease	7 (6%)

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The median age at the diagnosis was 10.6 years (range 1-17) and 68% of patients diagnosed at age 10 or older. Among our patients, 20 (17.3%) had extraosseous Ewing sarcoma (EES), while 95 (82.6%) had primary bone tumors. Among primary bone tumors, 32 (27.8%) were located in the lower extremities, 15 (13%) in the upper extremities, 14 (12.1%) in the pelvis, 19 (16.5%) in the ribs, and 15 (13%) in other bones. At the time of diagnosis, metastases were detected in 42 (36.5%) cases, with 18 (15.6%) having isolated lung metastases and 10 (8.7%) having isolated bone metastases. Upon examination of necrosis rates in materials obtained post-surgery, more than 90% necrosis was observed in 27 (23.4%) patients, while less than 90% necrosis was observed in 38 (33%) patients. Necrosis rates could not be determined in 14 (12.1%) patients due to irradiation, and data on necrosis rates were unavailable for 36 (31%) patients. When evaluated in terms of local treatments, total resection with mass excision was performed on all cases except for the three cases that were lost due to progressive disease. Local radiotherapy was applied to a total of 49 (42.6%) cases, including the three cases for which surgical treatment could not be performed. Among these cases, 38 (33%) had a low necrosis rate, 3 (2.6%) were not suitable for surgical treatment, and the remaining 8 (6.9%) cases received radiotherapy based on various reasons determined by the council.

Relapse was observed in 30 (26%) patients, with a median relapse time of 20 months (range 1-60 months). Isolated lung relapse was observed in 13 (11.3%) patients, while isolated local relapse was observed in 6 (5.2%) patients.

The mean follow-up duration for all cases was 44±38.3 months. Median duration was 34 months. Upon assessing their current status, complete remission was achieved in 58 (50.4%) patients, while 50 (43.4%) patients died during follow-up. Among those who died, 9 (7.8%) died due to sepsis and 32 (27.8%) due to progressive disease. For all cases, the 5-year OS and EFS rates were determined as 51% and 45%, respectively (Figure 1). Five year OS and EFS rates for the cases with LD were 66%, 56% while the cases with MD were 28%, 27% (p<0.001).

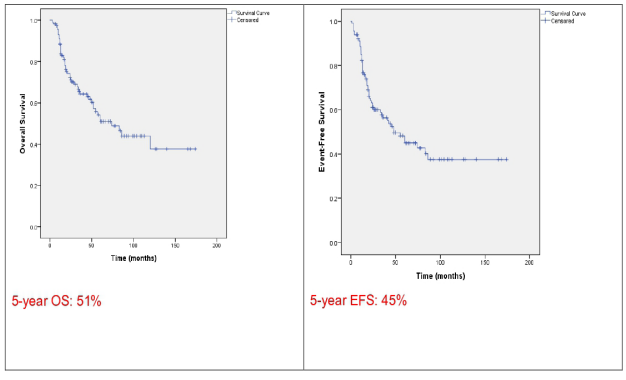

Figure 1. *Five year overall and event free survival rates of the patients with Ewing Sarcoma*

Table II. *Comparison of Overall and Event-Free Survival by Sociodemographic Characteristics (n=115)*

	Overall Survival			Event-free survival		
	Survival time (months)	P	Cumulative proportion surviving at the 5-years	Survival time (months)	P	Cumulative proportion surviving at the 5-years
Gender						
Male (n: 63)	101.8±10.3	0.241	55.3%	91.4±10.5	0.353	51%
Female (n: 52)	79.2±11.6		45.2%	71.8±11.7		37%
Age						
<10 years (n: 36)	106.7±12.3	0.090	59.7%	95.0±12.4	0.179	47.7%
≥10 years (n: 79)	82.2±10.2		46.2%	75.3±10.2		45%
Primary Tumor Site						
Bone (n: 95)	86.1±8.9	0.683	48.5%	77.0±8.5	0.349	41.1%
Lower ext. (n: 32)	78.5±9.4	0.821	53.4%	65.1±8.2	0.759	46.4%
Upper ext. (n: 15)	108.3±20.0		61.1%	82.5±21.2		43.1%
Pelvis (n: 14)	60.1±7.1		36.5%	49.7±9.3		26.7%
Costa (n: 19)	78.4±18.5		38.6%	70.5±18.2		35.4%
Other (n: 15)	72.0±14.8		44.8%	66.1±14.4		40.7%
Soft tissue (n: 20)	101.7±17.6		50.1%	101.2±17.7		58.7%
Metastasis						
None (n: 73)	116,5±10.7	**<0.001**	66.1%	108.2±9.9	**<0.001**	56%
Present (n: 42)	51.9±7.5		28.7%	45.2±7.6		27.4%
Metastasis Site						
Isolated Lung (n: 18)	46.1±9.7	0.354	21.7%	41.5±9.6	0.630	20.8%
Isolated Bone (n: 19)	37.8±11.0		30%	33.8±11.9		30%
Others (n: 15)	69.9±14.3		40%	55.7±15.1		34.9%
Necrosis Rate						
More than 90% (n: 27)	118.2±14.4	0.219	0.649±0.104	118.6±14.4	**0.026**	0.667±0.098
Less than 90% (n: 38)	74.0±9.0		0.469±0.097	57.1±8.7		0.316±0.089
Relapse						
None (n: 85)	113.7±9.4	**0.002**	65.1%	112.4±9.4	**<0.001**	64.4%
Present (n: 30)	51.2±7.3		22.7%	43.1±5.0		3.4%
Relapse Location						
Isolated Lung (n: 13)	35.6±5.5	0.159	7.7%	35.6±5.5	**0.049**	7.7%
Distant Bone Relapse (n: 11)	70.3±13.7		45.5%	53.8±9.6		9.1%
Local (n: 6)	44.3±13.9		25%	39.6±12.8		16.7%

When factors influencing survival were evaluated, gender, primary tumor site, and metastasis site did not have a statistically significant effect on survival (Table II). Children younger than 10 years of age had a higher survival rate than children older than 10 years but this difference was not statistically significant for OS and EFS (p=0.09). At the time of diagnosis, cases with MD had statistically significantly lower survival times (p<0.001,

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p<0.001) (Figure 2). When comparing patients with necrosis rates above 90% to those with rates below 90%, it was observed that patients with higher necrosis rates had longer survival times, although, this difference was not statistically significant for OS but significant for EFS (p=0.219, p=0.026). Since, the rate of bone necrosis could not be determined in cases with irradiated prostheses, the survival outcomes were compared with the survival outcomes of cases with reported necrosis rate. Cases with necrosis rate below 90% and irradiated cases were analyzed in pairs and it was found that cases with irradiated had longer survival time. This difference was not statistically significant (p>0.05). The cases with necrosis rate above 90% had longer survival time than irradiated cases, but this difference was not statistically significant (p>0.05).

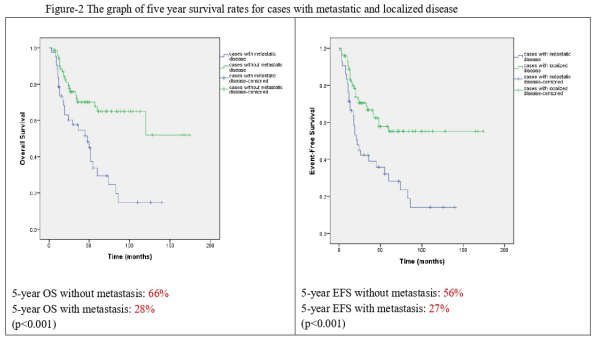

Figure 2. *The graph of five year survival rates for cases with metastatic and localized disease*

In the presence of relapse, 5-year OS and EFS rates were statistically significant lower in patients with relapse disease (p=0.002, p<0.001) (Figure 3). When comparing relapse locations (isolated lung, isolated bone, and local relapses) in patients, the difference was not statistically significant for OS, but the cases with isolated bone relapse had longer survival times than the others and this difference was statistically significant for EFS (p=0.049). Relapse disease was observed in 15% of the cases with EES, and the mortality rate was 45% in all cases. However, 40% of cases started treatment with metastatic disease at diagnosis.

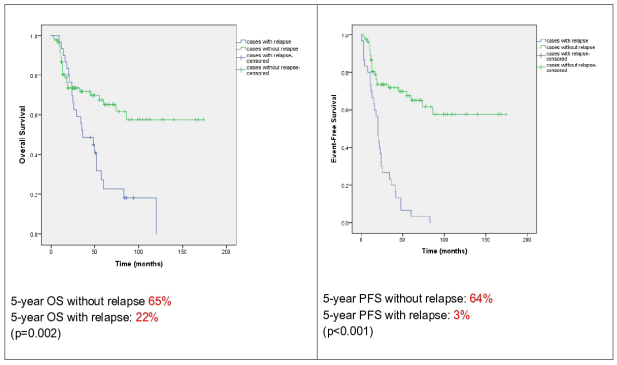

Figure 3. *The Graph depicts the 5-year survival rates of the cases according to the relapse disease.*

4. DISCUSSION

In our study, cases diagnosed with ES accounted for 13.8% of all cases diagnosed with malignancy. In the literature, the incidence rate during childhood is reported to be around 2-5%, and the higher prevalence in our hospital is attributed to our multidisciplinary approach involving the orthopedic and radiation oncology departments, which has established our hospital as a referral center for bone sarcomas. The peak age for childhood ES is reported as 15 years old, and it is usually seen in children over 10 years old [1,2]. In our study, the median age at diagnosis was 10.6 years, with 68% of cases diagnosed at age 10 or older, which is consistent with the literature. Upon evaluation, based on age groups, although, not statistically significant, survival times were found to be longer in cases diagnosed under the age of 10 compared to older children. Advanced age (age 14 years or 18 years) is also noted as a poor prognostic factor in previous studies [15-17].

In terms of gender, the incidence rate in male cases is approximately 1.5 times higher than in female cases [4]. Consistent with the literature, male cases were more frequently observed in our study as well. However, similar to the findings in the literature, gender did not have a statistically significant impact on survival [6].

Extraosseous ES cases constitute approximately 15-20% of all cases [7], and in our study, this rate was 16.3%. Generally, the prognosis is better for EES compared to ES originating from bone [8,18]. In a meta-analysis examining twenty-nine studies, the 5-year OS in pediatric EES cases was reported as 69%, with mortality and recurrence rates of 29% and 35%, respectively [19]. In our study, recurrent disease was observed in 15% of the 20 cases diagnosed with EES, and the mortality rate was higher (45%) in all cases. It is thought that the fact that 40% of cases started treatment with metastatic disease at diagnosis may have contributed to this rate. When considering its impact on survival, the survival times of EES cases were longer compared to cases originating from bone, although, this difference was not statistically significant. This may be attributed to the high incidence of metastatic disease at the time of diagnosis in our EES cases.

The most common sites of involvement are the lower extremities, pelvis, and ribs [20]. Our study showed that lower extremities are the most common site of involvement, followed by rib and pelvic involvements. In a study evaluating thirty-one cases, the frequencies of primary tumor sites were reported as extremities (51.6%), the thoracic cage (19.4%), and the pelvis (16.1%), which is similar to our study [21]. Axial tumor localization and pelvic involvement have been associated with poor prognosis [15,16], Our study showed that the shortest survival time was in cases with pelvic origin, although this difference was not statistically significant.

In our study, 35.8% of cases had MD, with the lungs being the most common metastatic site (72.7%), followed by bone metastases (47.7%). In a study evaluating twenty-four cases, the MD rate was 25%, with the lungs being the most common metastatic site [22]. The presence of MD at diagnosis is the most

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important poor prognostic factor [1], with OS rates reported as 20-30% [15,16]. In our study, the 5-year OS rates in MD and LD cases were 28% and 66%, respectively. This difference was statistically significant and was consistent with the literature.

Another important prognostic factor is the histopathological response to neoadjuvant chemotherapy, represented by the tumor necrosis rate [6]. In our study, the survival time of cases with a necrosis rate above 90% were found to be longer compared to those with a necrosis rate below 90%. In a study evaluating complete remission (100% necrosis) in 427 cases, patients with 100% necrosis had significantly higher survival rates compared to other cases [23]. In another study, the 5-year disease-free survival was significantly better in patients with <5% viable tumors than in patients with >30% viable tumors (75% vs. 20%, p<0.001) [24]. Consistent with this study, the necrosis rate exceeded 90% in approximately one-third of the cases, and these cases exhibited significantly longer event-free survival times in our research. In 14 cases (12.1%), the necrosis rate could not be determined due to the placement of irradiated endoprostheses. The cases with irradiated endoprotheses exhibited a longer survival time than the cases with necrosis rate below 90%, and a shorter survival time than the cases with necrosis rate above 90%. Despite this, the diffrences were not statistically significant. However, this is the first research that compares the outcomes of irradiated protheses with those of other prostheses.

In patients with relapse, the prognosis is very poor, and the survival rate is around 10-30%. Response to salvage therapy is also a prognostic indicator in this patient group [2]. In our study, relapsed disease developed in 26% of cases, with the lungs being the most common site of relapse (43.7%). Our local relapse rate was 18.75%. In cases with relapse, the 5-year EFS and OS rates were 16% and 22%, respectively. In our study, the survival rates in cases with relapse were significantly lower, which were consistent with the literature. In contrast to expectations, patients with isolated bone relapse exhibited longer survival times and rates compared to those with isolated lung relapse. It has been postulated that the increased mortality rate due to sepsis and respiratory distress contributed to the shorter survival times observed in our patients with isolated lung relapse. Limitations of our study include: its retrospective nature and the inability to measure tumor volume for all patients due to the unavailability of diagnostic imaging at the time of diagnosis.

Conclusion

Despite the implementation of multimodal therapies, the prognosis for childhood ES remains poor, particularly in cases where the disease has metastasised or relapsed. Consequently, the significance of prompt diagnosis to ascertain that these cases are diagnosed as non-metastatic remains paramount. Furthermore, there is a pressing need for the development of new treatment options for metastatic and relapsed cases. The potential for early detection and intervention to significantly impact the outcome of ES is clear, emphasising the importance of ongoing research and development of innovative therapies for better management of this disease.

Compliance with Ethical Standards

Ethics committee approval: Ethical approval was obtained from the Marmara University School of Medicine Non-interventional Clinical Research Ethics Committee (approval number: 09.2024.377). Consent for study participation was obtained from all patients or their guardians.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors contribution: NE and AGT: Concept and design, AGT and KT: Data Collection or processing, GT: Analysis or interpretation, NE and OS: Literature search, NE and ZO: Writing the manuscript. All authors approved the final version of the manuscript.

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Adenovirus pneumonia in an immunocompetent patient : A case report

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ABSTRACT

Adenoviruses are viruses that typically cause mild infections involving the upper or lower respiratory tract, gastrointestinal tract, or conjunctiva in children and immunocompromised patients. Severe pneumonia progressing to respiratory failure is very rare in healthy adults without underlying immunodeficiency.

In this article, a case of fulminant pneumonia caused by adenovirus in a 26-year-old immunocompetent male patient is presented. The patient, a pediatric resident, applied to our emergency department with cough, pharyngitis, myalgia and fever. He was hospitalized due to the development of tachypnea, dyspnea and somnolence during follow up. Adenovirus was isolated from the nasopharyngeal swab and stool of the patient who developed hypoxemia and had infiltrates on the chest radiograph. The case, that got well and was discharged after an 11-day hospitalization, has been discussed in line with previous studies.

Keywords: Adenovirus, Pneumonia, Immunocompetent, Immunocompromised

1. INTRODUCTION

Adenovirus causes mild, self-limited upper respiratory tract infections gastroenteritis, and conjunctivitis in infants and young children [1]. Occasionally, outbreaks of self-limiting adenovirus infections have been reported in soldiers and children [2]. Severe adenovirus infection resulting in morbidity and mortality is well defined in immunocompromised patients [3]. However, it is very rare in healthy adults without prior immunodeficiency [4]. More than 50 known serotypes and 7 subgroups (A-G) of human adenoviruses have been identified [5].

In this article, a case of severe adenovirus pneumonia in a healthy male patient who presented with rapidly developing respiratory failure and successfully recovered with supportive treatment is presented. The clinical features, radiological findings and results of severe adenovirus pneumonia cases reported in previous studies are summarized.

2. CASE REPORT

A 26-year-old male, a pediatric resident who takes oral antidiabetics due to insulin resistance, was admitted to our emergency department with complaints of fever, cough and shortness of breath. History of fever, cough, sore throat and malaise had started 5 days ago. In the patient's anamnesis there was no hemoptysis, chest pain, difference in diameter between his two legs, color change or swelling and recent long-term travel history. There was no history of exposure to birds or pet feeding. Furthermore, the patient had no abdominal pain or dysuria, but it was learned that he had soft stools 3-4 times a day for the last two days. On admission, the patient was febrile (39.5°C), tachycardic (113/min), and tachypneic (26/min). His blood pressure was 108/72 mm/Hg and oxygen saturation 92%. On physical examination, he had mild pharyngeal and tonsillar hyperemia and his conjunctivas was hyperemic. No rash or lymphadenopathy was detected. No jugular venous distention and pretibial edema were observed. Cardiac examination

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was normal. Lung auscultation revealed rhonchi and coarse crackles especially in the lower zones of the right lung. No features were seen in the rest of his systemic examination. In the laboratory examinations at admission, high white blood cell and lymphopenia were notable features in the hemogram, while C-Reactive Protein (CRP) was high and procalcitonin was negative, and there was hypoxemia in the blood (Table 1). Posteroanterior (PA) PA chest radiography revealed consolidation in the lower zone of the right lung (Figure I).

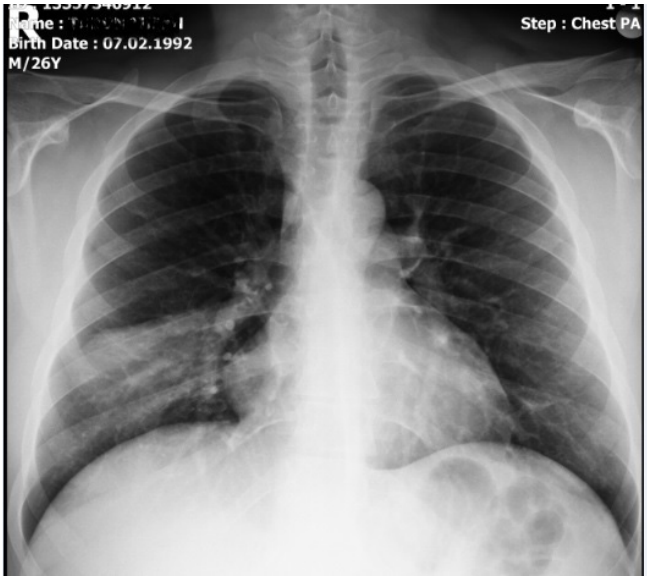

Figure I. *PA chest radiography findings at admission*

The patient was diagnosed with pneumonia and hospitalized. Blood , urine and sputum cultures were taken. Urine sample was also taken for Legionella and pneumococcal antigen tests. Empirical antibiotic therapy with ampicillin-sulbactam and clarithromycin was initiated. There was no growth in the cultures, urine Legionella and pneumococcal antigen tests were negative. The patient continued having fever in the following days despite treatment with antibiotics and antipyretics. His oxygen saturation decreased to 84%, tachycardia and tachypnea worsened. CRP and liver function tests (LFTs) increased (Table 1). Antibiotic therapy was changed to piperacillin-tazobactam. Considering that the patient was a pediatric resident, nasopharyngeal swab and stool samples were sent in order to study the molecular viral panel. Thorax computerized tomography (CT) scanning (Figure II) was also taken. Consolidation with air bronchograms involving almost the entire middle lobe was observed in the right lung and focal patchy infiltration areas with air bronchograms were observed in the left lung upper lobe's apicoposterior segment and lingula. Focal patchy parenchymal infiltration area was observed at the mediobasal segment of the right lung's lower lobe. An increase in reticular density was observed in the subpleural area posterobasal segment of the right lung's lower lobe. Human adenovirus (HAdV) was positive in the patient's nasopharyngeal swab and stool.

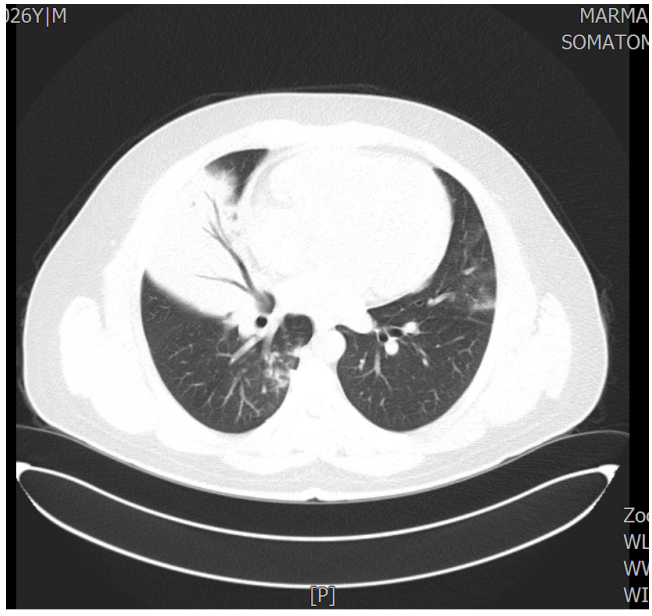

Figure II. *Lobar consolidation due to adenovirus pneumonia on thorax CT*

The patient was isolated and antibiotics were discontinued. 4-5 lt/min oxygen was given by nasal cannula. Fever was brought under control with supportive treatment, cold application and antipyretics. Eight days after hospitalization, the patient's general condition improved, fever and LFTs regressed. CRP levels and his oxygen requirement also decreased. Vital monitorization was continued. On the eleventh day, a control PA chest radiography (Figure III) was taken. The patient did not require oxygen and had no fever and it was observed that the consolidations had regressed. The patient was discharged successfully with outpatient polyclinic control recommendations.

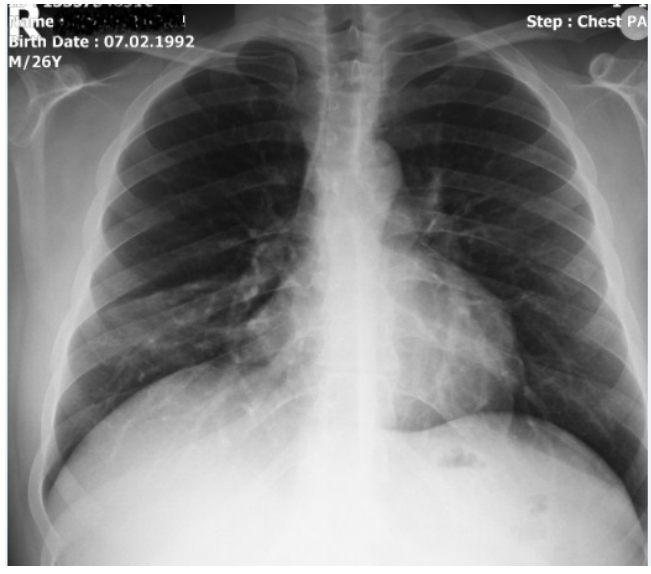

Figure III. *Post-treatment PA chest radiography*

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Table 1. Laboratory values of the patient

	On Admission	3rd Day of Hospitalization	11th Day of Hospitalization
Hematology			
White Blood Cell Count (WBC)	13200 µL	14600 µL	8200 µL
Neutrophils	12000 µL	11300 µL	4900 µL
Lymphocytes	700 µL	2600 µL	2700 µL
Eosinophils	0 µL	0 µL	100 µL
Basophils	0 µL	0 µL	100 µL
Monocytes	500 µL	600 µL	500 µL
Hemoglobin (Hb)	13.9 g/dL	12.3 g/dL	13.8 g/dL
Platelets	222000 µL	212000 µL	362000 µL
Serum Biochemistry			
Blood urea nitrogen (BUN)	12 mg/dL	8 mg/dL	8 mg/dL
Creatinine (CRE)	0.89 mg/dL	0.68 mg/dL	0.79 mg/dL
Aspartate aminotransferase (AST)	36 U/L	99* U/L	38 U/L
Alanine aminotransferase (ALT)	39 U/L	78* U/L	82 U/L
Lactate dehydrogenase (LDH)	382 U/L		
Albumin	4.2 g/dL		
Total protein	7.9 g/dL		
Sodium (Na)	140 mEq/L	136 mEq/L	
Potassium (K)	3.8 mEq/L	4.6 mEq/L	
Calcium (Ca)	8.4 mEq/L	8.5 mEq/L	
Glucose	103 mg/dL		
C-reactive protein (CRP)	88.10 mg/L	213* mg/L	5.72 mg/L
Procalcitonin	0.11 ng/mL	0.26 ng/mL	<0.020 ng/mL
Immunoglobulin G (Ig G)	16.33 g/L		
Immunoglobulin A (Ig A)	2.18 g/L		
Immunoglobulin M (Ig M)	2.18 g/L		
Total immunoglobulin E (Ig E)	5.31 IU/ml		
Arterial blood gas (room air)			
pH	7.48	7.43	7.44
Partial pressure of carbon dioxide (PaCO2)	33 mmHg	39 mmHg	45 mmHg
Partial pressures of oxygen (PaO2)	60 mmHg	50 mmHg	82 mmHg
Arterial oxygen saturation (SaO2)	92 %	84 %	96 %
Serum bicarbonate (HCO3)	24 mmol/L	25.6 mmol/L	30.2 mmol/L
Lactate	1.7 mmol/L	1 mmol/L	1.6 mmol/L
Base excess	1.3 mmol/L	1.8 mmol/L	5.5 mmol/L

3. DISCUSSION

Adenovirus is a non-enveloped double-stranded linear DNA virus. It can be transmitted to humans by direct contact, fecal-oral or droplet infection. The virus infects mucosal surfaces (gastrointestinal tract, respiratory system, conjunctiva, urogenital system). Fifty percent of adenovirus infections are asymptomatic. Clinical manifestations of symptomatic adenovirus infection includes pharyngoconjunctival fever, cryptictonsillitis, epidemic keratoconjunctivitis, swimming pool conjunctivitis, upper respiratory tract disease, pneumonia, hemorrhagic cystitis, infantile gatroenteritis, hepatitis, myocarditis and meningoencephalitis [2]. In our case, fever, cough, shortness of breath, sore throat and malaise was present and further examination and tests revealed pharyngoconjunctival hyperemia, fever and pneumonia.

Community-acquired pneumonia (CAP) is one of the leading causes of death worldwide. Respiratory viruses account for more than 22% of adult CAP cases. With the help of advances in molecular techniques, HAdV has been found to be increasingly involved in sporadic cases and severe CAP outbreaks in healthy adults [6]. Adenovirus pneumonia is very rare in immunocompetent adults. Even though, it usually shows a mild clinical course that is self-limiting, it can lead to severe epidemics and fatal results even in people with a healthy immune system. Adenovirus is an oncogene in animals but not in humans [7,8]. Outbreaks of adenovirus-related diseases have been described in adults and soldiers. An outbreak of respiratory disease, possibly caused by adenovirus B2 strain, was described in a military camp in Turkey [9].

Although, the immune system of our case was intact, he developed pneumonia. In previous studies, it is stated that adenovirus can cause serious respiratory tract infections in immunocompromised patients, but less is known about severe adenovirus pneumonia in immunocompetent adults. Cederwall et al., in a retrospective study, compared adenovirus-induced respiratory tract infections and pneumonia in immunocompromised and healthy adults in terms of clinical presentation and severity of infection. As a result, they showed that adenovirus can cause serious infections in both immunocompromised and healthy adults and the clinical presentation and the need for hospitalization, mechanical ventilation and antiviral treatment were equal in both groups [10].

Diagnosis of adenovirus infection is made by viral culture, viral antigen test, polimerase chain reaction (PCR) and serology. In our case, we detected adenovirus by PCR in the nasopharyngeal swab and positive viral antigen test in the stool. More than 50 known serotypes and 7 subgroups (A-G) of human adenoviruses have been identified. Adenovirus serotype was not studied in our case [7].

Generally, community-acquired viral pneumonia is caused by influenza, parainfluenza, respiratory syncytial virus, human metapneumovirus and adenovirus. Most of these agents cause bronchiolitis and bronchopneumonia. Lobar pneumonia usually suggests bacterial agents, but unlike other viral agents, adenovirus can cause consolidation [11]. There are studies

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showing that the predominant radiological sign of adenovirus pneumonia is consolidation. To date, it is the only virus with a major radiological finding of focal or lobar consolidation that mimmicks typical bacterial pneumonia [6,12]. In our patient's thorax CT findings: consolidation, patchy infiltration including air bronchogram was observed.

It is known that advanced age, diabetes, cardiovascular diseases and chronic respiratory diseases cause susceptibility to infectious diseases and a more serious disease course [13]. Many studies show that diabetes is associated with more severe disease and more mortality, especially during the COVID-19 pandemic [14]. Similarly, obesity has been shown to be associated with more severe disease and mortality in COVID-19. Impaired insulin secretion and insulin resistance form the basis of the pathogenesis of Type 2 diabetes [15]. However, there is insufficient evidence that insulin resistance alone causes viral pneumonia and severe disease course. Metformin and lifestyle change have long been used as initial treatment in Type 2 diabetes [16]. Diabetic patients treated with metformin have reduced mortality and complications from COVID-19 compared with patients receiving different or no treatment [17]. Our patient was using metformin due to insulin resistance.

A prospective cohort study that was conducted in China, in respiratory, paediatric, emergency/intensive care wards, participants were followed over 4 weeks for development of clinical respiratory illness. Nasopharyngeal swabs were obtained at baseline and at the end of the study. The primary endpoints were laboratory-confirmed bacterial colonisation and viral respiratory infection. Bacteria were isolated from 76.2% participants at baseline and 57% participants at the end of the study. Among all bacterial positive cases, streptococcus pneumoniae was the most commonly isolated organism at baseline (96%) and at the end of the study (72%). There were 15.7% laboratory confirmed viral infections found at baseline and 9.0% found at the end of the study. Rhinovirus/enterovirus was the most common viral pathogen accounting for 10.8% and 4.5% infections at baseline and at the end respectively. Other viruses detected included adenovirus, coronavirus, H1N1 and H3N2 influenza virus and human metapneumovirus [18]. Being a healthcare provider, our patient was at higher risk of getting respiratory infections.

Treatment of adenovirus may be in the form of supportive treatment and/or antiviral therapy. There are studies reporting positive results after cidofovir and ribavirin administration in immunocompromised patients. In these studies, antiviral therapy was tried in patients with abnormal laboratory findings (leukopenia, thrombocytopenia or elevated liver enzymes), progressive respiratory failure and patients who developed vasopressor and mechanical ventilation requirements and no complications were observed [19, 20]. We applied supportive and symptomatic treatment in our patient and followed up the improvement of his general condition by close vital monitorization without any antiviral therapy.

Conclusion

Today, viral agents, which are among the causes of community-acquired pneumonia, can also cause serious infections in the normal population. Therefore, in cases where there is no antibiotic response to the treatment of community-acquired pneumonia, it may be appropriate to consider viral causes during diagnosis, even if clinical and radiological findings suggest bacterial agents.

Compliance with Ethical Standards

This research was conducted ethically in accordance with the principles of Helsinki World Medical Association Declaration.

Patient consent: The patient gave his consent for clinical information relating to his case to be reported in a medical publication.

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

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Authors contributions: DV and ZO: Research idea, DV, ZO and SEE: Design of the study, DV, OA and NMC: Acquisition of data for the study, DV: Analysis of data for the study and drafting the manuscript, DV: Interpretation of data for the study, SEE: Revising the manuscript critically for important intellectual content. All authors reviewed the results and approved the final version of the article.

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Case Report

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Attention deficit hyperactivity disorder and specific learning disability co-occurring in a case with Silver-Russell syndrome

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ABSTRACT

This case presentation discusses the management of comorbid attention deficit hyperactivity disorder (ADHD) and specific learning disability (SLD) in a female adolescent diagnosed with Silver-Russell syndrome (SRS).

A 13-year-old female patient presented to the child psychiatry outpatient clinic eight months ago with complaints of reading and writing difficulties and forgetfulness. When she was four years old, she was diagnosed with SRS. Somatotropin therapy was initiated for the patient. Based on psychiatric examination, family interviews, psychometric assessments, and information obtained from school, the patient was diagnosed with ADHD and SLD. The patient was started on methylphenidate treatment, gradually titrated to a dose of 27 mg/day. She was also referred for special education for the SLD diagnosis. In the literature, it has been reported that in most children with SRS, intelligence is within the normal range, and they often receive diagnoses of ADHD and/or SLD. Studies have shown that although, executive function disorders are not significantly associated with SRS in comparison to control groups, there is an increased risk. Children and adolescents with this rare congenital disorder are at risk for psychiatric disorders, and periodic evaluation by a child psychiatrist is recommended.

Keywords: Silver-Russell syndrome, Attention deficit hyperactivity disability, Specific learning disorder, Child, Neurodevelopmental disorders

1. INTRODUCTION

Silver-Russell syndrome (SRS) is a heterogeneous congenital disorder characterized by growth retardation, low birth weight, short stature, and dysmorphic facial features. Approximately 60% of patients diagnosed clinically with SRS can have an underlying molecular cause identified. The most common underlying mechanisms include loss of methylation at chromosome 11p15 and maternal uniparental disomy for chromosome 7 [1]. The prevalence of the condition is estimated to be 1 in 30,000 to 1 in 100,000 live births [2]. Studies have shown that individuals with SRS are at significant risk for both motor and cognitive developmental delay, as well as learning difficulties [3]. Due to these risks, individuals with SRS need developmental assessments from infancy onward. Moreover, research has shown that negative body image concerns in children and adolescents with SRS can lead to psychosocial problems, anxiety disorders, social anxiety, and depression [4].

Attention deficit hyperactivity disorder (ADHD) is a mental disorder characterized by age-inappropriate attention problems, excessive motor activity, and/or impulsivity (such as inability to delay gratification, acting without thinking, and impulsivity) that become evident in preschool and school-aged children and persist throughout life. It is classified under the title "Attention-Deficit/Hyperactivity Disorder" in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). It has three subtypes: "Predominantly Inattentive Presentation," "Predominantly Hyperactive/Impulsive Presentation," and "Combined Presentation," which includes symptoms from both groups. According to DSM-5 criteria, for the predominantly inattentive presentation, at least six out of nine symptoms should be present; for the predominantly hyperactive/impulsive presentation, at least six out of nine symptoms should be present; and for the combined presentation, both sets of criteria should be met. Symptoms should be present in two or more settings before

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the age of 12 for at least six months and should impair social, academic, or occupational functioning. ADHD, one of the most common mental disorders in childhood, is associated with impairments in behavior, emotions, academic performance, and social functioning. When left untreated, it can lead to ongoing difficulties in adulthood as well [5, 6].

Specific learning disability (SLD) is a neurodevelopmental disorder that arises from the interaction of genetic, epigenetic, and environmental factors. In the DSM-5, learning disability is addressed in various subcategories, including difficulties in reading, reading comprehension, writing, written expression, understanding numbers and calculations, learning numerical reasoning, and academic skills. It involves challenges not only in academic areas but also in motor, sensory, and perceptual domains. Reading difficulty (dyslexia) is the most common among these disorders [5, 7].

Specific learning disability can be defined as specific deficiencies in perceiving and processing information. Additionally, individuals with SLD experience problems in auditory and visual perception, memory, fine and gross motor skills, attention, language and communication, abstraction, and social skills. Delay in language development, difficulty in word finding and naming, mixing up basic words, word-syllable conversion (e.g., saying "vami" instead of "mavi", saying "fison" instead of "sifon") difficulty in learning letter-sound relationships; difficulty in motor skills, inability to use scissors, inability to use fork and spoon, coordination difficulties, difficulties in understanding similarities and differences, and confusion in directions can be given as examples [8].

Due to its neurodevelopmental nature, SLD can exhibit different characteristics throughout life, starting from early stages of life. Studies in the literature have found that children with SRS have a higher frequency of SLD and ADHD disorder compared to the general population [9].

In this case presentation, the management of a female adolescent followed up with SRS diagnosis along with coexisting ADHD and SLD was discussed in light of the literature.

2. CASE REPORT

A thirteen-year-old girl was brought to the child psychiatry outpatient clinic eight months ago with complaints of difficulty in reading and writing and forgetfulness. It was learned from her medical history that she was born via cesarean section due to prematurity at 36 weeks of gestation following an uncomplicated and planned pregnancy. She was born weighing 2160 grams (-1.9 SDS) and measuring 43 cm (-2.3 SDS), and did not experience any perinatal or postnatal medical issues. It was learned that the patient, who was breastfed for about four months, started walking at fifteen months of age, began speaking meaningful single words at sixteen months of age, and received toilet training at the age of three. At the age of six, due to insufficient growth in height and weight, she was referred to pediatric endocrinology. During the physical examination, her weight was measured as 12.5 kg (-3.7 SDS) and her height as 96 cm (-4.1 SDS). Broad forehead, relative macrocephaly, and triangular facial appearance were observed, and the patient was diagnosed with Silver-Russell syndrome using the Netchine-Harbison clinical scoring system [1].

Recombinant growth hormone therapy (somatropin) for short stature, which she had been using for seven years, was stopped five months ago. In the family history, it was found that the mother, aged 31, is physically and mentally healthy, has a primary school education, and is a housewife; the father, aged 36, is physically and mentally healthy, has a high school education, and working in the auto electrical business to support the family. It was also noted that the patient's two brothers are healthy. No specific features are identified in the family history.

In the educational history, it was noted that the patient attended kindergarten for two years, had difficulty learning colors, numbers, and shapes, had good relationships with peers, did not have any separation anxiety from parents, learned to read and write in the second term of the first grade, but lagged behind peers in school subjects and literacy, is currently in the sixth grade with low academic performance, struggles to focus on lessons in class, easily gets distracted while studying, has difficulty sustaining attention on tasks, exhibits forgetfulness in completing household chores, and has trouble following teachers' instructions or completing school assignments properly.

In the psychiatric examination, it was observed that the patient's overall appearance appeared younger than her age, her self-care was appropriate for her age and sociocultural background, she was cooperative, her speech was coherent and goal-directed, her mood was euthymic and congruent with affect, her consciousness was clear, her orientation to person, place, and time was intact, her associations were organized, there were no perceptual disturbances, and, her intelligence level was clinically normal.

Upon examination of the Sentence Completion Test administered to the patient, it was observed that there were letter reversals, capitalization errors, and failure to leave spaces between words. According to information obtained from the school, it was revealed that the patient's academic performance was well below the class average, and she experienced difficulties in listening to, understanding, and interpreting information. The teacher-completed Turgay's DSM-IV ADHD and Disruptive Behavior Disorders Screening Scale (T-DSM-IV-S) [10] revealed a score of 21 out of 27 points on the attention deficit subscale, 4 out of 27 points on the hyperactivity and impulsivity subscale, 6 out of 24 points on the oppositional defiant disorder subscale, and 4 out of 45 points on the conduct disorder subscale.

T-DSM-IV-S completed by the patient's mother revealed a score of 18 out of 27 points on the attention deficit subscale, 2 out of 27 points on the hyperactivity and impulsivity subscale, 4 out of 24 points on the oppositional defiant disorder subscale, and 4 out of 45 points on the conduct disorder subscale. Higher scores are associated with greater symptom severity. According to the Wechsler Intelligence Scale for Children (WISC-R) [11] administered to the patient, the verbal IQ was 85, performance IQ was 85, and the total IQ was 85. In the clinical assessment of the patient's SLD, the Specific Learning Difficulties Clinical Observation Battery (SLD-COB) was administered [12].

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During the mathematics test, the patient made errors while doing addition using pen and paper, and also made errors in multiplication, whether mentally or using pen and paper. She read 72 words per minute, but comprehension was below average. According to the norm value for 5th grade Turkish children, 104.35±25.46 words per minute is considered normal [12]. In the writing test, she exhibited difficulties such as letter reversals, mixing upper and lower case letters, omitting punctuation marks, and not leaving spaces between words. Her clock drawing was inaccurate. She correctly distinguished between left and right, but showed differences in lateralization (preferring the right hand, left eye, and right foot). She made errors in prioritization and sequencing. According to the clinical assessment of the patient, difficulties were observed in the areas of reading, writing, and mathematics.

Based on the psychiatric examination, family interviews, psychometric assessments, and information obtained from the school, the patient was diagnosed with ADHD, predominantly inattentive presentation, and SLD with impairments in reading, mathematics, and written expression. The patient was referred to special education for a diagnosis of specific learning disorder. Furthermore, psychostimulant medication (methylphenidate HCL) therapy for ADHD was initiated, and the medication dose was gradually titrated up to 27 mg/day. At the patient's follow-up visit two months later, according to the information obtained from the school, the T-DSM-IV-S rating scale subtest scores showed improvement, with the inattention subscale score decreasing to 4, the hyperactivity-impulsivity subscale score decreasing to 0, the oppositional defiant disorder subscale score decreasing to 2, and the conduct disorder subscale score decreasing to 1. According to the T-DSM-IV-S rating scale-parent form, the inattention subscale score decreased to 3, the hyperactivity-impulsivity subscale score remained at 0, the oppositional defiant disorder subscale score decreased to 1, and the conduct disorder subscale score decreased to 1. On the other hand, although, the patient had been referred to special education due to SLD, it was learned that the family did not send the patient to special education because they thought there was no problem with her education. The family stopped the child psychiatry follow-ups at their own request.

Informed consent was obtained from the patient and parents for the case presentation.

3. DISCUSSION

Silver-Russell syndrome is a congenital condition characterized by significant growth retardation that persists both intrauterinely and postnatally, along with distinct physical features such as prominent forehead, micrognathia, ear anomalies, and a characteristic triangular face [13]. Growth hormone (GH) deficiency may be present in individuals with SRS who exhibit intrauterine growth retardation [14]. Although, GH deficiency was not detected in our case, she used somatropin for seven years due to short stature. Research indicates that individuals with GH deficiency may experience cognitive impairments, and GH therapy has been shown to partially improve these functions to some extent [15].

Reviewing the literature, it has been reported that in many children with SRS, intelligence is normal, and they often have diagnoses of ADHD and/or SLD [9]. However, additional studies are needed to elucidate the relationship between comorbid psychopathologies in this field. Treatment guidelines for ADHD in children and adolescents recommend psychosocial interventions initially for young children and older children with mild to moderate symptoms; for more severe ADHD symptoms, psychostimulants alone or in combination with psychosocial interventions may be necessary. Methylphenidate and dexamphetamine (or dextroamphetamine) are considered first-line treatments for children with ADHD [16].

The adverse effects of psychostimulant medications are generally dose-dependent and may include decreased appetite, abdominal pain, headache, irritability, anxiety, and sleep problems. Concerns may arise regarding the potential impact of methylphenidate treatment on growth and development in our case; however, a meta-analysis has shown that methylphenidate treatment does not affect growth or alter weight-for-age percentiles [17]. In our case, no changes in height or weight were observed during follow-up measurements.

In a study conducted by Bogdanov et al., which investigated 16 children with SRS referred due to attention problems and learning difficulties, 50% of the cases were diagnosed with both ADHD and learning difficulties, 37.5% had only language-based learning difficulties, and 12.5% were diagnosed solely with learning difficulties [9]. The disorder most commonly associated with SLD is ADHD [18]. The co-occurrence of these two disorders has been found to range from 7% to 92% in research studies. DuPaul et al., in their study, reported the frequency of co-occurring ADHD with SLD as 18-60% and found the prevalence of SLD in individuals with ADHD to be seven times higher than that of the general population [19]. In recent studies conducted in Türkiye, the frequency of ADHD co-occurring with SLD ranges from 42.4% to 84.6%, while the frequency of SLD co-occurring with ADHD is reported to be 23.6% [20]. Similarly, in our case, there is a co-occurrence of ADHD and SLD.

Individuals with ADHD experience difficulties in executive functions such as problem-solving, planning, organizing, maintaining flexibility, sustaining attention, and working memory [21]. Studies have shown that although there may not be significant executive function impairments in children and adolescents with SRS compared to control groups, there is an increased risk of such impairments [22]. Additionally, studies have shown that adolescents and adults with SRS may develop low self-esteem, anxiety disorders, and major depressive disorder due to their dysmorphic appearance [23, 24].

When reviewing the literature, it is observed that there has been a primary focus on medical symptoms and interventions related to SRS, with limited attention given to cognitive abilities, academic and social developmental needs. In future research involving individuals with SRS, systematic neuropsychological

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assessment should be considered to evaluate sensory and motor skills, cognitive level, and psychosocial adjustment. A better understanding of SRS, which affects individuals throughout their lives, is necessary, particularly in terms of the specific interventions needed in school settings, such as special education, speech therapy, vocational and physical therapy, social skills training, and/or counseling [25].

Given the high likelihood of psychiatric comorbidities in children and adolescents with the rare congenital disorder SRS, we believe that referring them to a child and adolescent psychiatrist for psychiatric evaluation and implementing early treatment interventions are crucial for the benefit of the cases.

Compliance with Ethical Standards

This research was conducted ethically in accordance with the principles of Helsinki World Medical Association Declaration.

Patient Consent: The patient and her guardian gave their written consent for clinical information related to this patient to be reported in a medical publication.

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

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Authors contributions: BGO: Conception and design, NDV and AA: Data collection, BGO and HA: Analysis and interpretation of results, NDV, BGO, AA and HA: Draft manuscript preparation. All authors reviewed and approved the final version of the manuscript.

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Case Report

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A two-headed accessory muscle on the sole of the foot

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ABSTRACT

Anatomical variations include the absence of a muscle or tendon or its presence as an accessory muscle or tendon. Clinically, anatomic variations play an important role in diagnosis and theraphy.

In anatomy dissection laboratory, during routine dissection for educational purposes, a 83 -year- old male cadaver was dissected and a two-headed accessory muscle was observed on the plantar surface of the left foot.

The medial and lateral heads of the muscle were observed close to the medial and lateral plantar neurovascular bundles. The accessory muscle was pierced by the tendon of the flexor digitorum longus muscle and both muscles were inserted to the distal phalanx of the fifth toe.

The variations of the accessory muscles should be taken into consideration in surgical interventions, since, they may change the course of the intervention or as in the case of abductor hallucis muscle, they may be used in reconstructive procedures as grafts. Therefore, it is crucial for surgeons, orthopedic physicians, and anatomists to have a detailed knowledge of the intrinsic muscles of the foot.

Keywords: Accessory muscle, Variation, Plantar surface

1. INTRODUCTION

The general anatomy of the plantar region muscles is well known and well-studied in the literature. Apart from the general muscular layer divisions, plantar muscle groups may be divided into central and peripheral muscle groups to clarify surgical approaches. In the peripheral group of muscles, there are medial and lateral groups, and these muscles insert into the proximal phalanges [1]. On the other hand, the central group comprises numerous muscles such as flexor digitorum brevis (FDB), quadratus plantae (QP), lumbricals, plantar interossei, and dorsal interossei. Additionally, the central group is divided into a superficial layer, which inserts into the middle phalanges, and a deep layer which inserts into the distal phalanges [2,3].

Flexor digitorum brevis splits into four tendons that run to the lateral four toes; the flexor digitorum longus (FDL) tendons lay deep to the tendons when they enter the digital tendinous sheaths. Each tendon splits around the matching FDL tendon at the bases of the proximal phalanges. The two slip then reconnect and partially decussate, generating a tunnel through which the FDL tendon passes to reach the distal phalanges. The FDB tendon splits again and joins to the middle phalanx's shaft on both sides [2]. The common variations in the literature are related to the lumbricals, dorsal interossei, FDB, and extensor digitorum brevis (EDB) muscle and the presence of accessory muscles. These variations may raise questions about the functional effects on the gait and tarsometatarsal joint. A study focused on the variable attachments of the plantar interosseus muscles on a female cadaver's sole [4].

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The intrinsic muscle variations of the sole of the foot are rarely encountered [5], but the presence of these variations may provide crucial information for clinical interventions such as flat foot reconstructions in the plantar region of the foot since, the variative anatomy would impact the clinical approach.

The variations of the intrinsic muscles of the foot, particularly those associated with the medial longitudinal arch, may influence the function and stability of the foot. For instance, the cross-sectional areas of abductor hallucis longus and the flexor hallucis brevis medial part can affect the muscle strength and postural balance [6].

Additionally, these variations may be related to nerve entrapments such as the medial plantar nerve entrapment observed in the variations of abductor hallucis and adductor hallucis muscles [7].

In this case report, a two-headed accessory muscle observed on the plantar surface of the foot during cadaver dissection and its relationship with the neuromuscular bundle is presented. To the best of our knowledge, this report is the first presentation of such a variation.

2. CASE-REPORT

An unusual variation in the intrinsic muscles of the foot was coincidentally discovered in an 83-year-old male, 10% formalin embalmed cadaver, during a demonstrational foot dissection session for undergraduate and postgraduate studies in the cadaver dissection laboratories of the institution.

During routine cadaver dissection, a two-headed accessory muscle was observed on the plantar surface of the left foot. Each dissection process was carried out in accordance with Grant's Dissector [8]. The skin, superficial fascia, plantar aponeurosis and FDB, were dissected, in that order. Detailed observations and measurements were made for the accessory muscle, including its origin, course, and insertion.

The medial head of the accessory muscle was observed to be originating from the FDL muscle, whereas the lateral head from the flexor digiti minimi brevis muscle (Figures 1,2). Both medial and lateral heads of the muscle were coursing close to the medial and lateral plantar neurovascular bundles. The accessory muscle was pierced by the tendon of the FDL muscle. Both muscles were inserted into the distal phalanx of the fifth toe (Figure 2). The length of the muscle and its tendon was approximately 108.85 mm and 67.18 mm, respectively.

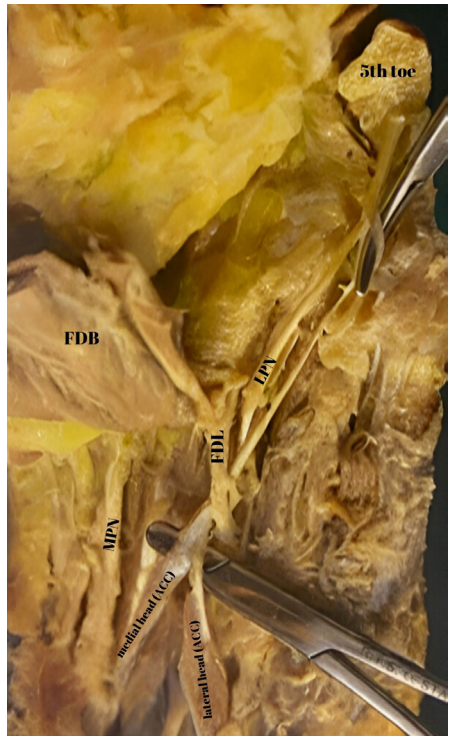

Figure 1. *ACC: Accessory muscle, MPN: Medial plantar nerve, LPN: Lateral plantar nerve, FDB: Flexor digitorum brevis muscle FDL: Flexor digitorum longus muscle*

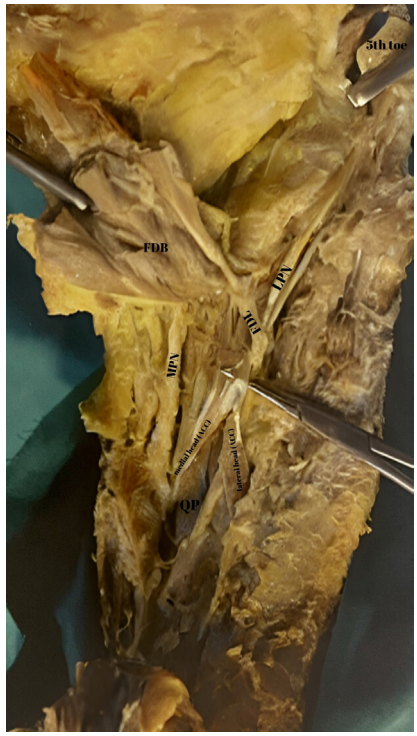

Figure 2. *QP: Quadratus plantae muscle, ACC: Accessory muscle, MPN: Medial plantar nerve, LPN: Lateral plantar nerve, FDB: Flexor digitorum brevis muscle FDL: Flexor digitorum longus muscle*

3. DISCUSSION

Accessory muscles have been identified as a possible source of clinical complaints, although, they are usually asymptomatic and discovered coincidentally [5]. Examples of accessory muscles in literature have anthropological significance as well as the ability to strengthen the parent muscle and be used as replacement flaps in tendon injuries. Tendon transfer of the FDL or flexor hallucis longus on the plantar surface of the foot is necessary to treat both Achilles tendon rupture and dysfunction of the posterior tibial tendon. To execute this surgical technique as effectively as possible, foot surgeons must thoroughly understand and assess the differences and relationships within the sole of the foot [9]. Symptomatic clawing of the fifth toe is a common presentation in clinical practice. Surgery is indicated when this condition does not respond to conservative treatment. However, if the tendon of an accessory muscle also inserts into the fifth distal phalanx, lengthening the FDL tendon may not result in satisfactory correction to clawing. In such cases, both tendons (FDL and accessory muscle tendon) must be lengthened to completely relax the clawed toe and allow definitive correction [10]. Holzmann et al., found an accessory muscle in the region and identified it as the flexor digitorum accessorius longus muscle [11]. Furthermore, Athavale et al., revealed that the medial head of the quadratus plantae muscle may possess distinct attachments [12]. Regarding the distinct attachments of the quadratus plantae muscle, Reeser et al., described that the variable insertion points might aggravate the symptoms of the tibial nerve lesions and the tarsal tunnel syndrome [13]. Recent studies emphasize that the accessory muscles may have close anatomical relations with the neurovascular bundles of the region, and this relationship may cause neuropathies and vascular insufficiencies due to entrapments or compressions of these bundles. For instance, the medial plantar nerve generally passes between the flexor hallucis and FDB, but rarely is observed to be coursing superficial to the FDB, provoking a nerve compression [14]. Hypertrophied abductor hallucis muscles may induce increased pressure on the medial plantar nerve, leading to pain and dysfunction [13]. Furthermore, variations and distinct insertions of the quadratus plantae may cause nerve entrapments and potentially contribute to tarsal tunnel syndrome [15].

Conclusion

The presence of accessory muscles and variations in the plantar region of the foot may have close anatomical relations with the neurovascular bundles. Such relations may cause neuropathies and vascular insufficiencies due to entrapments or compressions to the bundles. According to the results of the current study, the described accessory muscle may significantly contribute to the flexion of the toes and may alter the mechanics of walking. Furthermore, the variations of the accessory muscles should be taken into consideration in surgical interventions since, they may shape the course of the intervention. Finally, accessory muscles can be used as grafts for surgeries, such as the abductor hallucis muscle is frequently used in reconstructive surgeries.

Compliance with Ethical Standards

This research was conducted ethically in accordance with the principles of Helsinki World Medical Association Declaration.

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

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Authors contributions: The authors confirm contribution to the paper as follows: OK: Research idea, UV: Design of the study, EZ: Acquisition of data for the study, HE: Analysis of data for the study and drafting the manuscript, NY: Interpretation of data for the study, YA: Revising the manuscript critically for important intellectual content. All authors reviewed the results and approved the final version. OK: Final approval of the version to be published.

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