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Instructions to Authors

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Original Article

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A 10-day mild treadmill exercise performed before an epileptic seizure alleviates oxidative injury in the skeletal muscle and brain tissues of the rats

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ABSTRACT

Objective: Epileptic seizures may cause skeletal muscle injury and memory dysfunctions. The present study was aimed to investigate the possible protective effects of exercising prior to seizure on seizure-induced oxidative injury in the skeletal muscle and brain.

Materials and Methods: Sprague-Dawley male rats were assigned as non-exercise (n=16) and exercise groups (n=16). Following a 3-day exercise training, exercise protocol (30 min) was performed on a treadmill for 10 days, while control rats had no exercise. On the 11th day, the epileptic seizure was induced by a single intraperitoneal injection of pentylenetetrazol (PTZ) (45 mg/kg), while the control groups were injected with saline. Passive-avoidance test was initially performed before PTZ/saline injection and repeated 72 h later for the assessment of memory function. Brain and gastrocnemius muscles were taken for histological assessments and to determine the levels of malondialdehyde (MDA) and glutathione (GSH), myeloperoxidase (MPO) activity and luminal – and lucigenin – enhanced chemiluminescence levels.

Results: Exercise training alone increased the formation of reactive oxygen species and elevated the antioxidant GSH capacity of the muscle tissue in the control rats, but these effects were not observed in the muscles of the exercised rats induced with a PTZ-seizure. On the other hand, short-term exercise alone had no effect on the basal oxidative parameters of the brain tissues. Prior exercise did not alter the average seizure scores or memory performances when compared to non-exercised groups, but suppressed the PTZ-induced elevations in MDA and chemiluminescence levels as well as MPO activity in the brain.

Conclusion: A 10-day mild treadmill exercise reduced the oxidative brain damage due to a single seizure-induced excitotoxicity and exerted a preconditioning effect on the skeletal muscles exposed to tonic-clonic contractions.

Keywords: Epileptic seizure, Exercise, Oxidative damage, Memory dysfunction, Skeletal muscle

1. INTRODUCTION

Status epilepticus (SE) is a common life-threatening neurological emergency characterized by a prolonged seizure, which results in excitotoxicity-induced cerebral injury [1]. Neuronal hyperexcitability during SE causes oxidative stress, presenting with increased generation of reactive oxygen species (ROS), lipid peroxidation [2], and consequently with neuronal degeneration that includes the hippocampal areas, resulting in cognitive dysfunction and deficits in memory and learning [3-6]. Apart from the brain tissue, generalized excessive muscle contractions in SE affect all the organ systems, particularly the over-working skeletal muscles [7]. Moreover, increased load on the skeleton due to exaggerated muscle contractions during seizures may even cause fractures, skeletal muscle damage, and rhabdomyolysis [8-11].

In contrast to limited information confirming the prevalence of physical exercise as a seizure-triggering factor and the lack of any mechanistical explanations regarding how exercise could induce seizures [12], exercise was commonly suggested to have several beneficial effects on the outcomes of epileptic seizures in both humans and animals. Although the available studies on the effects of physical activity on seizure frequency are heterogeneous, many human studies have generally reported

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that regular physical exercise can reduce the seizure frequency and improve cardiovascular and psychological health of epileptic patients [13]. Moreover, exercise can exert beneficial actions such as reductions in seizure susceptibility, anxiety and depression, and consequently leading to improvement of life quality of individuals with epilepsy, which suggests that exercise can be a potential candidate for the non-pharmacological treatment of epilepsy [13, 14]. Accordingly, animal studies have shown that exercise performed before or after the induction of seizure has positive effects on SE. In the early stages of life, long-term memory deficit caused by SE and the occurrence frequency of seizures after SE were reported to be reduced in exercised rodents [15, 16]. Various exercise regimens were reported to increase latency to SE development, decrease susceptibility to subsequently induced seizures and ameliorate the course of experimentally induced SE [17, 18].

In rats, both a preconditioning exercise performed before the induction of ischemic brain injury [19] and an exercise performed for neurorehabilitation during post-ischemic recovery [20] were shown to reduce oxidative brain damage and associated cognitive dysfunctions. Similarly, exercise training was proven to stimulate several cellular adaptive events in the skeletal muscle to resist against any injurious insults to the muscle fibers [21]. However, the putative protective role of exercise on the seizure-injured neuronal and muscular tissues was not elucidated before. Thus, our study was aimed to evaluate the possible protective effects of exercising prior to seizure on the seizure-induced oxidative injury of the brain and skeletal muscle.

2. MATERIALS and METHODS

Animals

Sprague-Dawley male rats (240-260 gr) used in the study were supplied by the Marmara University Animal Center (DEHAMER). The rats had free access to a standard rat chow and water, and were kept under laboratory conditions with controlled humidity, temperature (22 ± 0.5°C) and light/dark (12/12 h) cycles. All experimental protocols, guided by the National Institute of Health guidelines for the Care and the Use of Laboratory Animals, were approved by the Marmara University Animal Care and Use Committee (approval code: 77.2017.mar; date: 6.11.2017).

Experimental design and exercise

The rats were randomly assigned to either non-exercise (n=16) or exercise groups (n=16) (Fig. 1). In the exercise groups, initially a 3-day adaptation period for 10 min/day was allowed for the rats to get accustomed to the exercise procedure by placing them on a rodent treadmill (TME 9805, Commat Instruments, Ankara, Turkey). After the acclimatization period, the exercising rats ran on a treadmill at 0° of inclination initially at a speed of 10 m/min (first 3 days) and then at 11.6 m/min (following 7 days) speed for 30 min/day for 10 days [22], while the sedentary rats had no exercise training. Following the 10-day exercise training period, an epileptic seizure was induced on the 11th day by the intraperitoneal injection of pentylenetetrazol (PTZ), while the control groups were injected with saline. Since the aim was to evaluate only the preconditioning effects of exercise on seizure-induced oxidative damage, exercise was discontinued during the 3 days following saline or PTZ injection. Passive avoidance test (PAT) was performed on two occasions, immediately before and at the 72th h of PTZ-seizure, to assess the memory function of the rats. The rats were decapitated after the second PAT performance. Brain and gastrocnemius muscle tissues were collected for histological assessments and to determine the levels of malondialdehyde (MDA) and glutathione (GSH), myeloperoxidase (MPO) activity and chemiluminescence levels of luminol and lucigenin as indicators of reactive oxygen species (ROS) generation.

Seizure induction and assessment

The rat was placed in a Plexiglas observation box (38 × 30 × 25 cm) and a single dose of PTZ (45 mg/kg) was injected intraperitoneally to induce an epileptic seizure [23]. Epileptic seizures were recorded by a video camera for 30 minutes. The intensity of the recorded seizures was evaluated using Racine's scoring system (0-5), where 0, no behavioral changes; 1, focal facial movements with twitching of ears and whiskers; 2, myoclonic jerks but no rearing up; 3, myoclonic jerks with rearing up; 4, clonic convulsions along with posture loss; 5, generalized tonic-clonic seizures [24].

Evaluation of memory function

In order to evaluate the effects of exercise on seizure-induced memory dysfunction, PAT was performed using an electronic two-compartment box (Northel Passive Avoidance System, Istanbul, Turkey) composed of an illuminated compartment, a dark compartment and a guillotine gate separating these compartments. On the 11th day of the experimental procedure, all rats underwent the first PAT before PTZ or saline injection (Fig. 1), which was accepted as the acquisition trial of the test [25]. Then, the recall phase of PAT was performed at the 72nd hour of seizure induction just before euthanasia. In the acquisition trial, the rats were placed individually in the illuminated compartment of the box, and due to their inborn tendencies for preference of dark areas, they moved from the illuminated compartment into the dark side and a guillotine door between two chambers was closed. By the electric grid floor of the dark compartment, a mild inescapable electrical foot shock (0.3–0.6 mA) was applied for 5s, and the rat was then taken out from the box, where it has learned the negative outcomes of entering the dark chamber. Then, 72 h after this acquisition trial, the rat was put again into the illuminated compartment and the latency to pass to the dark compartment was recorded to assess the memory performance. If the rats have avoided entering the dark chamber with a latency over 300 s (cut-off point), it was considered as a normal memory performance, while a shorter latency to enter the dark chamber was regarded as poor memory collection [26]. During each of the PAT applications, both compartments were cleaned with 70% alcohol before the next animal was placed in the box.

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Measurement of myeloperoxidase activity, malondialdehyde and glutathione levels in the skeletal muscle and brain

Biochemical measurement of MPO activity in a tissue reflects the magnitude of neutrophil infiltration and correlates positively with the histochemically recorded neutrophil infiltration to that tissue [27]. Based on H2O2-dependent oxidation of o-dianisidine.2HCl, MPO activity in both the skeletal and brain tissues was determined using a spectrophotometer at 460 nm, and the MPO activity was expressed as units per gram tissue [28]. For the determination of MDA and GSH levels, tissue samples were homogenized in trichloroacetic acid solution (10 %) and centrifuged for 15 min at 3000 g and 4°C. The supernatants were mixed with thiobarbituric acid to determine the MDA levels (U/g tissue) as the by-products of lipid peroxidation [29]. GSH levels (nmol/g tissue) in the muscle and brain tissues were determined using a modified Ellman procedure. The absorbance was measured at 412 nm and the amount of GSH was given as µmol (g /tissue) [30].

Chemiluminescence assays

Chemiluminescence (CL) assay is a frequently used noninvasive method for the direct assessment of the levels of ROS using a luminometer (Junior LB 9509, EG&G, Berthold, Germany) at room temperature. Lucigenin-(bis-N methylacridinium nitrate) probe specifically detects superoxide radicals, while luminol-5-amino-2,3-dihydro 1,4 phthalazinedione) is used commonly for the detection of OH, H2O2 and HOCl radicals [31]. Using these probes, ROS generation was assessed in both the muscle and brain tissues and CL levels were calculated by linear approximation. ROS generation in terms of CL was expressed as the area under the curve (AUC) of relative light unit per mg tissue [32].

Histopathological examination

Gastrocnemius muscle samples obtained from the experimental groups were fixed in 4 % paraformaldehyde, processed for routine histological procedures and embedded in paraffin (Leica TP1020 and EG1150H+C). Paraffin sections of 5µm-thick were cut by a rotary microtome (Leica RM2125RT) and stained with hematoxylin and eosin (H&E) for the light microscopic examinations. The histological features of the muscle sections were evaluated regarding the organization of fibers and the presence of inflammatory cell infiltration and congestion. Myofibers presenting with typical peripheral nuclei were observed in the healthy fibers, whereas centralized nuclei were regarded as a sign of the repairing process of damaged myofibers [33-35].

Following their fixation in 4 % paraformaldehyde, brain tissues were incubated in 20 % sucrose solution at +4°C and were then kept at – 20°C until they were cut by a cryostat (Leica CM1950, Germany). Five µm-thick frozen sections taken from the hippocampus and cortex were stained with cresyl violet (Nissl staining) for light microscopic examinations. Microscopic appearances of the neurons and the intensity of dark neurons were examined to assess the extent of neuronal injury [36-38].

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 8.0.2 program (GraphPad Software, San Diego, CA, USA). All data are presented as means ±SEM. Analysis of the biochemical data was performed by using one-way ANOVA followed by post-hoc Tukey test. Values of $p < 0.05$ was considered as statistically significant.

3. RESULTS

Following PTZ injection, except for a single rat in the exercised PTZ group that had no seizures at all, the rest of the rats in the non-exercised and exercised groups demonstrated either twitches or tonic-clonic contractions. The averages of the stage scores reached in the exercised and non-exercised groups were similar (Table I). Average seizure scores, the numbers of rats recorded at stages 4 and 5, and the total duration of contractions during stages 4 and 5 were similar in the non-exercised and exercised rats, showing no difference due to the 10-day exercise performed before an epileptic seizure.

On the acquisition trial of the PAT, no significant differences were observed among the initial latency periods of rats (data not shown). At the recall phase of the PAT, none of the rats in the control groups, either sedentary or exercised, have entered the dark chamber within the cut-off period (300 ± 0). However, three rats in the sedentary-PTZ rats have entered the dark chamber, while all the rats in the exercise-PTZ group avoided entering into the dark compartment, but no statistically significant difference was observed between the latency periods of the non-exercised or exercised PTZ groups (Table I).

Table I. *Seizure scores and passive avoidance test (PAT) results of the rats injected with PTZ*

	Seizures			PAT
	Average of stage scores (1–5)	Number of rats at stage 4-5 (n; %)	Total time spent at stage 4-5 (sec)	Retention latency (sec)
No exercise	3.88 ± 0.58	5/8; 62.5 %	224.4 ± 91.3	232.5 ± 43.5
Exercised	3.50 ± 0.76	5/8; 62.5 %	231.6 ± 107.2	300 ± 0

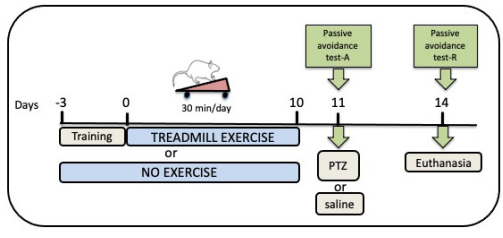

Figure 1. *Schematic explanation of the experimental procedures. A: acquisition phase, R: recollection phase of the passive avoidance test.*

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Exercise alone had no effect on the oxidative parameters measured in the brain tissues of control rats (Figure 2). However, induction of a PTZ-seizure resulted in the elevation of brain MPO activity, MDA levels, luminol and lucigenin CL levels in the non-exercised rats (p<0.01-0.001), while a 10-day exercise performed prior to seizure induction suppressed these elevations significantly (p<0.01), demonstrating the inhibitory effect of exercise on oxidative brain damage and associated neutrophil infiltration caused by PTZ-seizure. On the other hand, antioxidant glutathione levels in the brain tissues were not altered by neither exercise nor seizure induction.

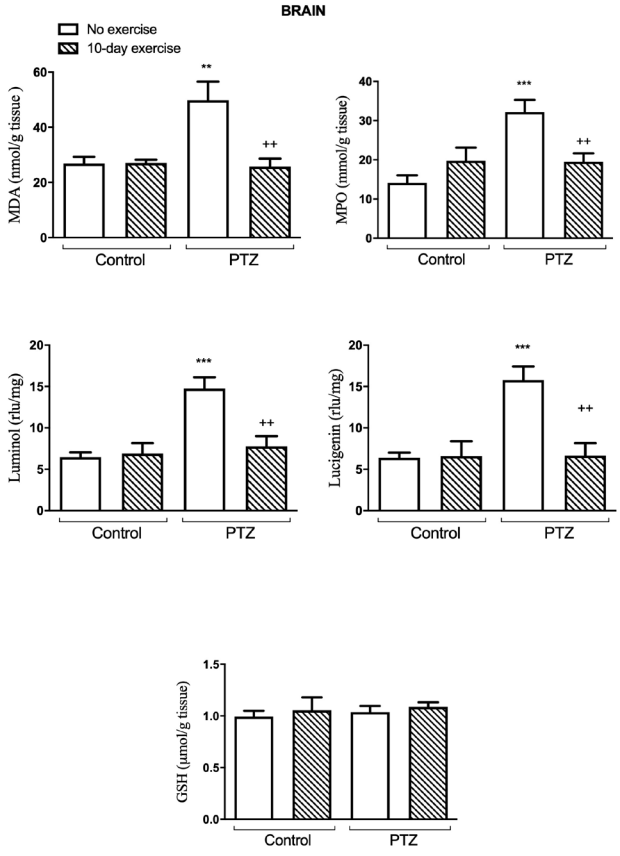

Figure 2. *Malondialdehyde (MDA), myeloperoxidase (MPO) activity, glutathione (GSH) content and luminol or lucigenin-enhanced chemiluminescence levels in the brain tissues of the control and PTZ-seizure groups that have not exercised or had a 10-day treadmill exercise. **p<0.01, ***p< 0.001, compared to non-exercised control group; ++p<0.01 compared to non-exercised PTZ group.*

Similar to that observed in the brain tissue, MDA levels and MPO activity in the gastrocnemius muscle of the control rats were not altered by exercise training (Figure 3). However, exercising for 10 days elevated the generation of ROS in the gastrocnemius muscle, as assessed by elevated levels of luminol – (p<0.01) and lucigenin-(p<0.05) enhanced CL, which was accompanied by an increase in the antioxidant GSH content (p<0.05). Although PTZ-seizure in the non-exercised rats did not increase muscle tissue MDA level, it resulted in increased levels of luminol-enhanced CL (indicative of OH−, H2O2, HOCl radicals) (p<0.01) with a concomitant elevation in the MPO activity (p<0.001). On the other hand, having exercised prior to PTZ-seizure depressed MPO activity (p<0.01), showing the inhibitory effect of prior exercise on neutrophil infiltration to the muscles that have exhibited tonic-clonic contractions. Despite that exercise in the control rats had a stimulatory impact on antioxidant capacity of the skeletal muscle, PTZ-induced muscle contractions have not changed muscle GSH content in either non-exercised or exercised rats as compared to that of the control rats.

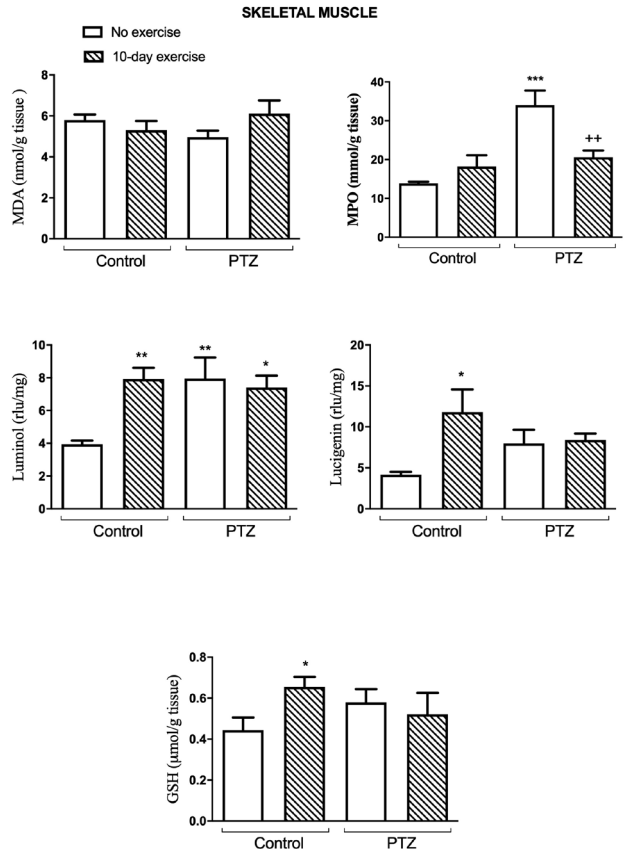

Figure 3. *Malondialdehyde (MDA), myeloperoxidase (MPO) activity, glutathione (GSH) content and luminol or lucigenin-enhanced chemiluminescence levels in the gastrocnemius muscle tissues of the control and PTZ-seizure groups that have not exercised or had a 10-day treadmill exercise. *p<0.05, **p<0.01, ***p<0.001, compared to non-exercised control groups; ++p <0.01 compared to non-exercised PTZ group.*

Examination of the H&E-stained sections of gastrocnemius muscles showed that most of the myofibrils exhibited normal regular morphology with peripherally located nuclei in both the non-exercised and exercised control groups (Figure 4), except for some muscle fibers of the exercised control group presenting with a few abnormally located nuclei, indicating the recovery of the injured muscle tissue [39]. On the other hand,

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in the non-exercised group induced with PTZ, myofibrils with abnormal organization, severe congestion and inflammatory cell infiltration were observed, whereas mild congestion and more regular myofibrils were evident in the exercised PTZ group.

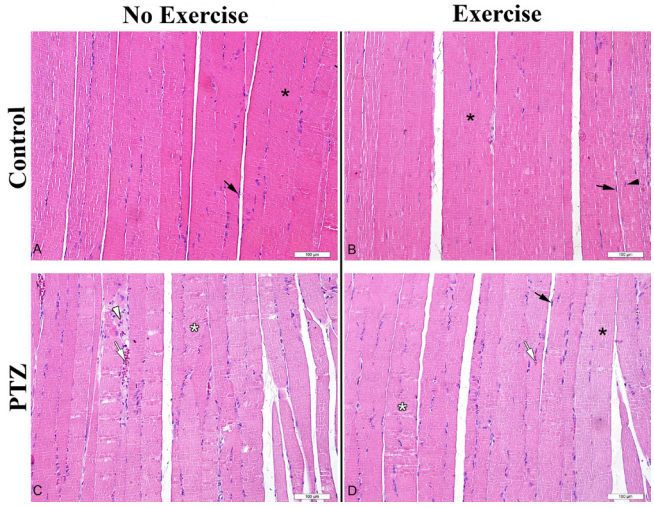

Figure 4. *Representative micrographs of the muscle tissues of the experimental groups. Arrow: peripherally located nucleus. Asterisk (*): muscle fiber with regular organization. Arrowhead: centrally located nucleus. White asterisk: muscle fiber with an abnormal organization. White arrow: vascular congestion. White arrowhead: inflammatory cell infiltration in the connective tissue. Hematoxylin and eosin staining.*

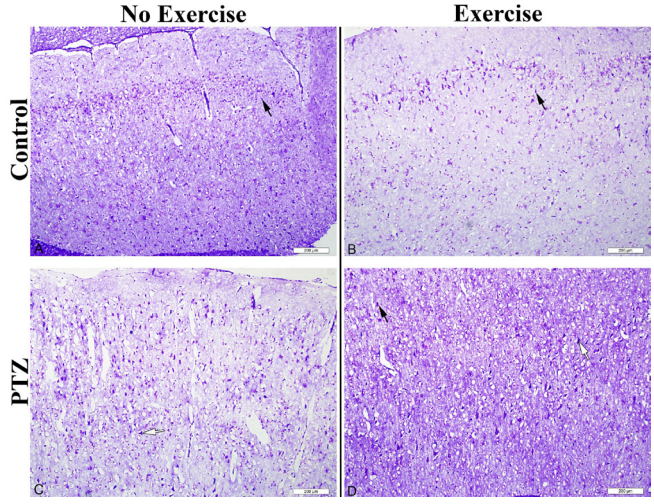

Figure 5. *Representative micrographs of cortical regions of the experimental groups. Arrow: regular-shaped neurons. White arrow: Dark neurons with shrunken cell bodies. Cresyl Violet staining.*

The evaluation of cresyl violet-stained brain sections of the exercised and non-exercised groups revealed that the neurons in both hippocampus and cortex were round or oval in shape, and consisted of blue nuclei with clearly visible borders, while no remarkable differences were observed between the morphological features of the brains of the exercised or non-exercised control rats (Figures 5 and 6). In the non-exercised group induced with PTZ-seizure, neuronal loss was evident in the dentate gyrus and cornu ammonis regions of the hippocampus, while the strongly stained and shrunken dark neurons were increased in number. In both the hippocampus and cortex, the number of pyramidal neurons and granular cells with indistinguishable borders of the nuclei and the cytoplasm were increased. On the other hand, neuronal morphology in the exercised PTZ group was similar to that observed in the brains of the control rats.

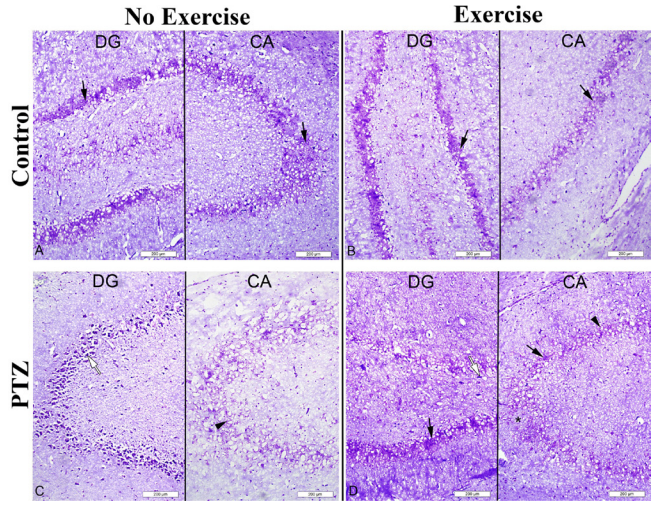

Figure 6. *Representative micrographs of the hippocampal regions of the experimental groups. Arrow: round – or oval-shaped neurons. DG: Dentate gyrus; CA: Cornus Ammonis. Arrowhead: degenerated neurons with unclear nuclei and cytoplasms. White arrow: dark neurons with shrunken cell bodies. Asterisk (*): neuron loss. Cresyl Violet staining.*

4. DISCUSSION

The findings demonstrated that the frequency of tonic-clonic contractions, average seizure scores and memory performances were similar in the non-exercised and exercised groups induced with a PTZ-seizure. Although, exercise training alone increased the formation of ROS and elevated the antioxidant GSH capacity of the muscle tissue in the control rats, these effects were not observed in the muscles of the exercised rats induced with a PTZ-seizure, suggesting that the upregulated GSH provided by prior exercise is depleted to overcome the oxidative injury of the muscle due to its exaggerated activity during seizure. Thereby, exercise prior to seizure was able to suppress PTZ-induced elevation in neutrophil infiltration, demonstrating the preconditioning effect of exercise in alleviating seizure-induced oxidative injury of the overworked muscles. In contrast to the skeletal muscle, short-term exercise alone had no effect on the basal oxidative parameters of the brain tissues. However, a 10-day mild exercise performed prior to PTZ-seizure was able to reverse the increased lipid peroxidation and ROS generation as well as neutrophil infiltration to the inflamed brain tissue,

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reducing the oxidative brain damage due a single seizure-induced excitotoxicity.

Several neuroprotective and anti-epileptogenic drugs have been examined for seizure prevention and treatment [23, 40]. Among these treatments, physical exercise has been investigated as an effective non-pharmacological complementary therapy for its potency in preventing the occurrence of seizures and in improving the comorbidities of epilepsy [41]. Accordingly, moderate exercise in rats was shown to decrease the spike amplitude and frequency of penicillin-induced seizures [42]. On the other hand, several clinical or experimental studies have suggested that exercise does not significantly affect the nature of seizures. Arida et al., have reported that an acute running exercise for 40 min in rats did not affect the number of stimulations required to initiate the first generalized seizure [43]. Similarly, it was reported that exercise performed by the epileptic patients has not affected the frequency of their seizures, but had a positive impact on their behavioral states [44]. Furthermore, physical training has been shown to enhance learning and memory in people with epilepsy [45, 46], which was also verified in several animal models [15, 47], suggesting that exercise, owing to its beneficial effects on the cognition and psychology of patients with epilepsy, could be recommended as a life-style change. However, our present results have indicated that a 10-day mild treadmill exercise performed prior to a single seizure did not alter the severity of that seizure and had no impact on the memory function, which was not altered by that single seizure. This discrepancy with the previous studies may be related with the duration and intensity of exercise, as well as the seizure model. On the other hand, our microscopic results revealed that the PTZ-induced degeneration observed in the hippocampal and cortical neurons was abolished in the brains of the exercised rats, indicating that the injury in the microscopical level has not reached to any alteration in the memory function, but along with the addition of other injurious seizures long-term effects of these neurodegenerative changes could be expected to affect the memory function. Since the repetitive epileptic seizures would disturb memory function, regular exercise for longer periods could have a better chance to provide a significant improvement in cognitive functions.

Despite that the performed exercise prior to a PTZ-seizure had no impact on the severity of the seizure, our results have demonstrated that exercise prevented oxidative injury of the brain, as assessed by the suppression of ROS generation, lipid peroxidation and neutrophil infiltration. Overproduction of free radicals due to neuronal hyperexcitability plays a central role in the pathogenesis of epilepsy. Increased production of ROS along with attenuated antioxidant defense makes the brain highly vulnerable to oxidative damage [48]. Since, oxidative damage can alter neuronal functions, the extent of the oxidative stress plays the major role in the pathogenesis and complications of seizure-induced cognitive dysfunctions, including learning and memory disorders [49-51]. We and the others have previously reported that epileptic seizure induced by a single dose of PTZ enhanced lipid peroxidation and neutrophil recruitment, exaggerated ROS generation, while endogenous GSH was depleted in the brain [23, 52, 53]. In the present study, we demonstrated that excess ROS generation in conjunction with increased lipid peroxidation and neutrophil infiltration were reversed by prior exercising demonstrating the neuroprotective effect of exercise, while the antioxidant GSH stores were kept unchanged. In a similar study, in which rats were injected with kainic acid to induce seizure, the expressions of the antioxidants superoxide dismutase and catalase were reduced in the hippocampus, while the antioxidants were elevated in the rats subjected to a treadmill exercise for 4 weeks, showing the preconditioning effect of exercise in suppressing oxidative stress by increasing hippocampal antioxidant enzymes [54]. It appears that this preconditioning effect of exercise becomes vital in maintaining oxidant-antioxidant balance upon an inflammatory challenge, as it is observed in seizure-induced neurotoxicity. On the other hand, exercise preconditioning was also shown to reduce neuroinflammation in a traumatic brain injury model by suppressing neutrophil infiltration [55]. When taken together with the associated reports, our data implicate that the neuronal oxidative damage produced by a single generalized seizure could be totally suppressed by exercise, suggesting that regular exercising in epileptic patients would have benefit in maintaining the oxidant-antioxidant status against the cumulative neurotoxicity due to repetitive epileptic seizures.

Depending on the training load, physical exercise can have positive effects on muscle function, while overproduction of ROS by a strenuous exercise can cause oxidative muscle damage [56]. In the current study, mild treadmill exercise for 10 days has enhanced generation of ROS with a concomitant increase in the endogenous antioxidant GSH levels, without causing any change in lipid peroxidation or neutrophil recruitment to the exercising muscle. Thus, it seems likely that the 10-day training has triggered ROS production and antioxidant capacity, which is expected to protect the exercised muscle from any upcoming oxidative challenges. Depending on the intensity of exercise, studies have reported that the endogenous antioxidants could be decreased or increased without any alteration in lipid peroxidation levels [57]. Although, high intensity exercise was shown to elevate myeloperoxidase activity in the gastrocnemius muscle [58, 59], the mild exercise in our study has not significantly affected the infiltration of neutrophils to the muscle, suggesting that a mild exercise is effective in upregulating the antioxidant content of the muscle without initiating any inflammatory response. On the other hand, exaggerated contraction of the muscle due to a PTZ-induced seizure in the current study has increased ROS generation, which was accompanied by the accumulation of neutrophils, while the GSH upregulated by exercise was used up to prevent any change in lipid peroxidation and to depress neutrophil infiltration. Thus, preconditioning of the muscle by prior exercise has increased the availability of the antioxidants to resist the oxidative injury evoked by generalized muscle contractions. In support of these biochemical data, our histological findings also revealed that abnormal organization of myofibrils and inflammatory cell infiltration in the muscles of the non-exercised PTZ rats were replaced by more regular myofibrils and a milder inflammation when the PTZ-rats have

previously exercised. Due to the forces generated in the muscles during tonic-clonic seizures, epileptic patients have a high risk for severe musculoskeletal injury [60] and even rhabdomyolysis resulting in acute renal failure [61]. Although it is well known that patients experience severe pain following violent tonic-clonic contractions, oxidative injury of the muscle induced by the seizure was not thoroughly investigated before. Therefore, our results verified for the first time that a single seizure enhances ROS generation and neutrophil accumulation, and initiates a local inflammatory response, which could give rise to soreness and pain experienced in the contracted muscles. Moreover, our results further showed that exercised and thereby preconditioned muscle could resist to the seizure-induced inflammatory insult.

In conclusion, the findings of the present study demonstrated that a mild exercise helps to maintain the oxidant-antioxidant balance in both the skeletal muscle and brain tissues against any forthcoming injurious incidents, and this preconditioning effect of exercise could be of vital importance in protecting the muscle and brain functions of the epileptic patients exposed to repetitive tonic-clonic contractions.

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Compliance with Ethical Standards

Ethical Approval: This study was approved by Marmara University Animal Care and Use Committee (approval code: 77.2017.mar).

Financial Support: No specific funding was received.

Conflict of Interest: There are no conflicting interests.

Author Contributions: SAT: Data acquisition (animal work, biochemical analyses). OTCK: Data acquisition (histological preparation and analyses). MY: Data acquisition (chemiluminescence analyses). AY: Design of work, data interpretation, critical revision of the manuscript. BCY: Design of work, data interpretation, critical revision of the manuscript. All authors contributed to the drafting of the manuscript and approved the final version of the article.

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The role of myocardial performance index and Nt-proBNP levels as a marker of heart dysfunction in nonalcoholic cirrhotic patients

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ABSTRACT

Objective: Cardiac dysfunction has been reported in both cirrhotic and alcoholic patients. Our aim was to determine the relation of serum N-terminal pro-B-type natriuretic peptide (Nt-proBNP) levels to myocardial performance index (MPI) and disease severity in nonalcoholic cirrhotic patients.

Patients and Methods: In this prospective study including 25 cirrhotic patients and 27 healthy controls, MPI was assessed by pulsed-wave tissue Doppler imaging (PW-TDI). The disease severity was determined by Child–Turcotte–Pugh (CTP) and model for end-stage liver disease (MELD) scores.

Results: There were no statistically significant differences in MPI levels between patients and controls (p< 0.246). Nt-proBNP levels (p< 0.0003), cardiac output (CO) (p< 0.0002), left ventricular end-systolic (LVES) volume (p< 0.031) and QT interval (p< 0.0001) increased and left ventricular systolic function was normal in all cirrhotic patients when compared to controls. Nt-proBNP levels were positively correlated with MELD scores (p< 0.0001, r= 0.59), QT duration (p< 0.0001, r= 0.59), CO (p= 0,001, r= 0.44), right atrial (RA) area (p= 0.026, r= 0.31) and negatively correlated with diastolic BP (p= 0.015, r= – 0.34).

Conclusion: We conclude that in nonalcoholic cirrhotic patients, left ventricular MPI and systolic function were normal. Nt-proBNP levels were correlated with the disease severity and hyperdynamic circulation.

Keywords: Cirrhosis, Heart failure, Nt-proBNP, Echocardiography

1. INTRODUCTION

Cirrhosis is characterized by hyperdynamic circulation with increased cardiac output, heart rate and a decreased systemic vascular resistance. Impaired cardiac contractility and performance in patients with cirrhosis has been termed 'cirrhotic cardiomyopathy' [1].

Alcohol is toxic to many organs including the liver and heart. Chronic alcohol abuse may induce hypertrophy, apoptosis and necrosis of myocytes and leads to both systolic and diastolic cardiac dysfunction and ultimately left and right ventricular dilatation [2].

Brain natriuretic peptide (BNP) which is secreted from ventricles in response to pressure and volume overload is a sensitive marker for heart disease. It relaxes vascular smooth muscle, causes arterial and venous dilation and leads to reduced blood pressure. It is secreted as pre-pro-BNP which is subseqently cleaved to proBNP, N-terminal pro-B-type natriuretic peptide (Nt-proBNP) and biologically active BNP [3]. Increased levels of BNP are related to diastolic cardiac dysfunction [4-6] and to the severity of the disease in patients with cirrhosis [4, 7-10]. High level of BNP is an independent predictor of mortality in cirrhotic patients [9, 11].

Myocardial performance index (MPI) described first by Tei and his co-workers is a new Doppler-derived index reflecting systolic and diastolic function of the heart. This simple and reproducible technique is not affected by heart rate, blood pressure, ventricular loading conditions [12]. It can be measured either by pulsed-wave Doppler (PWD) or pulsed-wave tissue Doppler imaging (PW-TDI). Both methods have high diagnostic accuracy for congestive heart failure, but conventional PWD may be affected by heart rate variability [13].

There have been few studies investigating the role of MPI in cirrhotic patients [10, 14-17].

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The aim of this study was to investigate the role of both MPI, measured by PW-TDI and Nt-proBNP levels on the assessment of cardiac function in nonalcoholic cirrhotic patients.

2. PATIENTS and METHODS

The study was designed as a prospective, clinical study involving the analysis of Nt-proBNP levels and echocardiographic evaluation of MPI in cirrhotic patients and controls. Twenty-five patients with liver cirrhosis and 27 controls were enrolled in the study. Diagnosis of cirrhosis was based on clinical, biochemical, endoscopic and ultrasonographic criteria.

Patients suffering from diseases potentially associated with high BNP levels including heart failure unrelated to liver disease, arterial hypertension, renal failure, respiratory failure, obesity (body mass index> 30 kg/m^2), diabetes, severe anemia (Hg< 7 g/dL), were excluded from the study. Patients with electrocardiographic and with echocardiographic evidence of structural heart disease and patients with alcohol dependence were also excluded from the study. All patients had normal cardiac physical examination and were in sinus rhythm at admission. Patients with bundle branch block, atrioventricular block, atrial fibrillation and pacemaker rhythm on electrocardiography were excluded from the study.

Patients were classified according to their Child–Turcotte–Pugh (CTP) scores as Stage A, B and C [17], then model for end-stage liver disease (MELD) scores were calculated. Stage A patients were compensated and Stage B and C patients were decompensated patients.

Echocardiographic Assessment

All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography [18,19]. M-mode, two-dimensional echocardiography, pulsed wave Doppler, continuous-wave Doppler and tissue Doppler studies were performed using a commercially available echocardiograph operating at 2,5-3 MHz.

Two-Dimensional Doppler Echocardiography

M-mode images were used for the measurement of left ventricular (LV) dimensions at end – diastole in the parasternal long-axis view. Left ventricular ejection fraction (LVEF) and left ventricular volumes were assessed by the biplane method of disks (modified Simpson's rule). The left ventricular mass (LVM) was calculated according to Cube formula and LVM index (LVMi) was defined as the ratio between LVM and body surface area. Left atrial volume (LAV) was calculated by area-length technique and was indexed to body surface area (LAVi). By planimetric method right atrial (RA) area was measured in the apical 4-chamber view at end-systole just prior to tricuspid valve opening and the area under the tricuspid valve annulus was excluded. Right ventricular (RV) area was measured by manually tracing RV endocardial border from the lateral tricuspid annulus to the apex and back to medial tricuspid annulus at end-diastole in RV focused apical 4-chamber view. Papillary muscles, moderator band and trabeculations were included in the cavity area.

Pulsed-wave Doppler examination of mitral inflow was performed in the apical 4-chamber position during quiet respiration by placing the Doppler sample volume in the middle of the LV inflow tract 1 cm below the plane of mitral annulus between the mitral leaflet tips. Maximal flow velocity in early diastole was recorded and velocity of the mitral inflow early, rapid-filling wave (E), the peak velocity of the late filling wave due to atrial contraction (A), and the E/A ratio were obtained.

Cardiac output (CO) was calculated as Doppler estimated time velocity integral (TVI) of the aortic systolic flow multiplied by cross-sectional area of the aorta and the heart rate. The aortic TVI was recorded from the apical 5-chamber view by placing the continuous-wave Doppler sample volume at the level of the aortic annulus, approximately 3-5 mm proximal to the valve. The diameter of the aortic annulus (D) was measured by recording the parasternal long-axis view in systole and CO was calculated using the following formula: $CO = 0.785 \times D^2 \times TVI \times$ heart rate [20].

Pulsed – Wave Tissue Doppler Imaging

Pulsed-wave tissue Doppler imaging was performed by placing the sample volume at the lateral corner of the mitral annulus from the apical 4-chamber view during quiet respiration. To display tissue velocities the gain was minimized and the wall filter settings were adjusted to exclude high frequency signals. Annular early (e') and late (a') diastolic velocities were measured. The transmitral E/e' ratio was calculated. To determine the MPI, the time interval from the end to the onset of the mitral annular velocity pattern during diastole (a) and the duration of the S-wave (b) were measured. MPI was calculated as (a–b)/b [21].

Left ventricular diastolic dysfunction (LVDD) was classified into four categories as: normal diastolic function $E/A > 0.75$ and $E/e' < 10$; mild LVDD, $E/A \leq 0.75$ and $E/e' < 10$; moderate LVDD, $E/A \leq 1.5$ and $E/e' \geq 10$; severe LVDD, $E/A > 1.5$ and $E/e' \geq 10$ [22].

All measurements were averaged from three consecutive cardiac cycles and an investigator blinded to all data performed the echocardiographic and electrocardiographic analyses.

Resting 12-lead surface ECG was obtained from all subjects at a speed of 25 mm/s with an electrocardiograph. QT interval was calculated manually by measuring the interval from the onset of the QRS complex to the end of the T wave. Three consecutive Q-T intervals were measured in each lead and were averaged. If a U wave was present, the Q-T interval was measured from the onset of QRS complex to the nadir of the curve between the T and U waves.

Biochemical Assays

In all patients venous blood samples were drawn into ethylenediaminetetraacetic acid (EDTA) containing tubes and plasma was removed by centrifugation and was frozen at – 80 C before analysis. Nt-proBNP serum level was estimated using an electrochemiluminescent immunoassay kit – (analisator MODULAR ANALITICS E 170, Roche Diagnostics GmbH, D-68296 Mannheim, Germany). Measurement range was of 5–35000 pg/ml. Normal values were < 125 pg/ml. Peripheral

venous blood samples were used for all estimations and biochemical analyses were performed using standard methods.

The study was approved by the Clinical Research Ethics Committee of Marmara University, School of Medicine, Istanbul (03 – 2006-0124), and informed written consent was obtained from all the participants.

Statistics Analysis

Statistical analyses were performed using Prism software (GraphPad Prism 6.0, USA; serial no. GPM6-131891-RJJW-4325E). Descriptive data were presented as percentage and mean±standard deviation. The Mann-Whitney U test was used to compare continuous variables in two independent groups and Kruskal-Wallis test was used to compare continuous variables in three independent groups. Dunn's multiple comparison test was used for post hoc analyses. Spearman's correlation was used to assess the correlation of continuous variables. A p value < 0.05 was considered as statistically significant.

3. RESULTS

The study group comprised 25 patients, 10 women and 15 men with an average age of 47.88±14.34 years. The control group included 27 healthy participants, 13 women and 14 men with an average age of 43.88±8.41 years. The causes of cirrhosis were hepatitis B virus infection-associated post-hepatic cirrhosis in 13 patients, hepatitis C virus infection in 6, and cryptogenic cirrhosis in 6 patients. Among them, 5 patients exhibited ascites, 4 experienced gastrointestinal bleeding, 1 had encephalopathy, 2 experienced spontaneous bacterial peritonitis, and 12 patients had a history of propranolol treatment. The cirrhotic patients were categorized as A (n= 15), B (n= 6) or C (n= 4) according to their CTP scores.

Demographic, clinical and biochemical characteristic of the cirrhotic patients and control groups are given in Table I. Plasma Nt-proBNP levels of cirrhotic patients were found to be significantly elevated than those of control participants (63.92 ± 18.45 vs 45.74 ± 8.62, p< 0.0003). Mean MELD score, aspartate aminotransferase, alanine aminotransferase, international normalized ratio, total and direct bilirubin levels in cirrhotic patients were also significantly higher than those in controls (p< 0.05). Albumin, hemoglobin, thrombocyte, and leukocyte values in cirrhotic patients were significantly lower than those in controls (p< 0.05) (Table I).

Echocardiographic and electrocardiographic parameters of cirrhotic patients and controls are shown in Table II. There was no statistically significant difference in MPI levels between patients and of controls (p> 0.05). Only left ventricular end-systolic (LVES) volume and CO were higher in cirrhotic patients than in controls (p< 0.05). Left ventricular end-diastolic (LVED) volume and LVMi were also higher in cirrhotic patients compared to controls, but the differences were not statistically significant. Additionally, QT intervals were also higher in cirrhotic patients (p< 0.05). (Table II).

Clinical, biochemical, echocardiographic and electrocardiographic parameters of compensated and decompensated patients and controls are presented in Table III. In post-hoc analysis Nt-proBNP levels, CO, LAVi, LVED volume and QT interval of decompensated patients were significantly higher than those of controls (p< 0.05). Additionally, LAVi and E/e' ratio were significantly higher in decompensated patients than in compensated patients (p< 0.05). Diastolic BP was lower in decompensated patients compared to controls (p< 0.05). (Table III).

Table I. *Demographic, clinical and biochemical parameters in cirrhotic (n= 25) patients and controls (n= 27)*

Characteristics	Cirrhosis (n=25)	Control (n=27)	p*
Age	47.88 ± 14.34	43.88 ± 8.41	0.387
Systolic blood pressure (mmHg)	120.60 ± 10.83	122.70 ± 8.27	0.365
Diastolic blood pressure (mmHg)	76.00 ± 5.00	78.46 ± 3.68	0.053
Pulse (beats/min)	72.32 ± 10.46	68.96 ± 9.62	0.325
MELD score	12.17 ± 4.43	6.35 ± 056	< 0.0001
Nt-proBNP (pg/ml)	63.92 ± 18.45	45.74 ± 8.62	< 0.0003
Sodium (mEq/L)	138.2 ± 4.22	139.9 ± 2.71	0.071
Creatinine (mg/dL)	0.82 ± 0.22	0.88 ± 0.14	0.188
Hemoglobin (gr/dL)	12.56 ± 1.68	13.62 ± 1.50	0.024
Trombocyte (10^3/μL)	76.264 ± 28.87	289.07 ± 69.49	< 0.0001
Leukocyte (10^3/μL)	3.989 ± 1.457	6.100 ± 1.359	< 0.0001
Aspartate Aminotransferase (U/L)	53.24 ± 24.01	30.73 ± 5.05	< 0.0001
Alanine Aminotransferase (U/L)	50.36 ± 35.59	32.81 ± 6.69	0.032
Total Bilirubin (mg/dL)	1.94 ± 1.36	0.63 ± 0.18	< 0.0001
Direct Bilirubin (mg/dL)	0.66 ± 0.68	0.20 ± 0.17	< 0.0001
Albumin (gr/dL)	3.72 ± 0.73	4.60 ± 0.47	< 0.0001
International Normalized Ratio	1.38 ± 0.31	0.96 ± 0.10	< 0.0001

** Mann-Whitney U test, Nt-proBNP: N-terminal propeptide of the brain natriuretic peptide; MELD score: model for end stage liver disease*

Table II. *Echocardiographic and electrocardiographic parameters of cirrhotic patients and controls*

Parameters	Cirrhosis (n=25)	Control (n= 27)	p*
MPI	0.32 ± 0.09	0.27 ± 0.11	0.246
LAVi (ml/m^2)	29.80 ± 10.55	23.57 ± 3.79	0.055
RA area (cm^2)	16.37 ± 4.14	14.27 ± 2.56	0.116
RV area (cm^2)	24.37 ± 3.58	24.37 ± 3.58	0.678
IVS (mm)	9.67 ± 1.34	9.07 ± 2.09	0.350
PW (mm)	9.31 ± 1.31	8.59 ±1.98	0.186
LVMi (gr/m^2)	101.00 ± 19.71	93.23 ± 25.11	0.057
LVED volume (ml)	118.80 ± 34.95	99.54 ± 19.46	0.055
LVES volume (ml)	46.58 ±16.03	38.21 ± 10.47	0.031
LVEF %	61.60 ± 6.97	61.81 ± 5.99	0.777
CO (L/min)	5.57 ± 1.24	4.32 ± 0.71	0.0002
E/A	1.34 ± 0.35	1.38 ± 0.33	0.784
e'(cm/s) lateral mitral annulus	12.40 ± 2.49	12.63 ± 2.66	0.993
E/e'	6.95 ± 2.05	6.38 ± 1.56	0.398
QT interval (msec)	424.90 ± 22.93	396.20 ± 16.58	0.0001

** Mann-Whitney U test, LAVi: left atrial volume index, RA: right atrium, RV: right ventricle, IVS: interventricular septum, PW: posterior wall, LVMi: left ventricular mass index, LVED: left ventricular end-diastolic, LVES: left ventricular end-systolic, LVEF: left ventricular ejection fraction, CO: cardiac output, MPI: myocardial performance index*

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Left ventricular systolic function was normal in all cirrhotic patients, but one patient (CTP A) exhibited mild, one patient (CTP B) exhibited moderate and one patient (CTP B) exhibited severe diastolic dysfunction.

Plasma Nt-proBNP levels were positively correlated with MELD scores (p< 0.0001, r= 0.59), QT duration (p< 0.0001, r= 0.59), CO (p= 0.001, r= 0.44), RA area (p= 0.026, r= 0.31) and were negatively correlated with diastolic BP (p= 0.015, r= – 0.34).

Table III. *Clinical, echocardiographic and electrocardiographic parameters of cirrhotic patients and controls according to Child–Turcotte–Pugh score*

Parameters	CTP Stage A (n= 15)	CTP Stage B+C (n= 10)	Control (n= 27)	p#
Systolic blood pressure(mmHg)	120.70 ± 9.17	120.50 ± 13.13	122.70 ± 8.27	0.657
Diastolic blood pressure(mmHg)	77.86 ± 4.26	73.64 ± 5.05	78.46 ± 3.68	0.010
MELD score*,**	9.69 ± 2.56	15.09 ± 4.46	6.35 ± 0.56	< 0.0001
Nt-proBNP (pg/ml)*	58.72 ± 19.51	70.06 ± 15.79	45.74 ± 8.63	0.0004
LAVi (ml/m^2)*,***	23.59 ± 7.09	37.70 ± 8.89	23.57 ± 3.80	0.0003
RA area (cm^2)	14.72 ± 3.80	16.58 ± 4.85	14.32 ± 3.33	0.389
RV area (cm^2)	26.09 ± 4.29	23.15 ± 4.40	24.37 ± 3.58	0.238
IVS (mm)	9.39 ± 1.41	10.17 ± 1.26	9.13 ± 2.04	0.188
PW (mm)	9.15 ± 1.31	9.53 ± 1.33	8.59 ± 1.98	0.327
LVMi (gr/m^2)	97.56 ± 17.86	105.40 ± 21.91	93.23 +25.11	0.136
LVED volume (ml)*	107.1 ± 26.53	133.8 ± 39.71	99.54 ± 19.46	0.043
LVES volume (ml)	43.45 ± 13.69	50.57 ± 18.49	38.21 ± 10.47	0.055
LVEF %	60.21 ± 6.87	63.36 ± 7.00	61.81 ± 5.99	0.567
CO (L/min)*	4.80 ± 0.86	6.33 ± 1.28	4.30 ± 0.70	< 0.0001
E/A	1.29 ± 0.38	1.40 ± 0.32	1.38 ± 0.33	0.442
e'(cm/s) lateral mitral annulus	13.08 ± 1.94	11.54 ± 2.91	12.63 ± 2.67	0.316
E/e'***	6.01 ± 1.19	8.27 ± 2.32	6.38 ± 1.56	0.025
MPI	0.31 ± 0.08	0.32 ± 0.09	0.27 ± 0.11	0.502
QT interval (msec)*	414.50± 19.19	436.20 ± 21.95	396.20 ± 16.58	< 0.0001

#Kruskal-Wallis test, CTP B+C vs control, ** CTP A vs control, *** CTP A vs CTP B+C*

MELD score: model for end-stage liver disease, Nt-proBNP: N-terminal propeptide of the brain natriuretic peptide, LAVi: left atrial volume index, RA: right atrium, RV: right ventricle, IVS: interventricular septum, PW: posterior wall, LVMi: left ventricular mass index, LVED: left ventricular end-diastolic, LVES: left ventricular end-systolic, LVEF: left ventricular ejection fraction, CO: cardiac output, MPI: myocardial performance index

4. DISCUSSION

Cirrhotic patients have hyperdynamic circulation characterized by increased cardiac output, decreased peripheral vascular resistance and increased plasma volume [1, 23]. We observed hyperkinetic circulation with increased CO and LVED volume in decompanseted cirrhotic patients. In this patient group, diastolic blood pressure decreased probably due to lowered peripheral resistance [23]. Decreased peripheral resistance and low blood pressure may activate renin angiotensin and aldosterone system which may further increase renal sodium and water reabsorption and intravascular volume. Angiotensin and aldosterone have been implicated in collagen accumulation in myocardial interstitium, myocardial hypertrophy and fibrosis [1]. Indeed, in our cirrhotic patients we observed statistically nonsignificant increase in LVMi. Echocardiographic parameters showing diastolic dysfunction were all in normal limits except for 3 patients. In advanced stages of cirrhosis LAVi increased significantly and although it was within normal limits, E/e' ratio also increased. Wiese et al., also showed a nonsignificant increase in the E/e'ratio with a-24 month follow-up of cirrhotic patients [24]. It was reported that transmitral E/e' ratio correlated well with left ventricular end diastolic filling pressure [25]. Increased LAVi and E/e' ratio are well known indicators of myocardial stiffness and developing diastolic dysfunction. In the literature, diastolic dysfunction was most prominent in patients with severe hepatic fibrosis and decompansation [4] and in these patients the combination of myocardial hypertrophy, diastolic dysfunction [6] and increased heart volumes may lead to cirrhotic cardiomyopathy.

In our study, left ventricular systolic function was normal in patient group when compared with controls. Barbosa et al., showed that 38% the patients with normal systolic function at rest developed systolic dysfunction during dobutamine infusion and the etiology of cirrhosis was alcohol in 77% of the patients [26].This may either indicate that classical echocardiographic examination is not sufficient enough to reveal mild systolic dysfunction and pharmacological stress can easily unmask left ventricular contractile problems or myocardial toxic effects of alcohol may have a significant role in decreased contractile reserve during dobutamine infusion. Similarly, Pimenta et al., found that CO measured by impedance cardiography decreased in patients with cirrhosis, 63% of whom were alcoholic [11]. In another study, conducted by Saner et al., 10 patients developed systolic dysfunction after liver transplantation and 2 patients known to use alcohol died due to congestive heart failure. Again, in this study, the main cause of cirrhosis in 29.9% of the patients was alcohol consumption [27].

The MPI has been shown to be useful in evaluating left ventricular function and prognosis of patients with heart-related disorders. The MPI, reflecting both the global systolic and diastolic cardiac function [12] was not higher in our cirrhotic patients than in controls. The most important reason for this was that our patients with a mean MELD score of 12.7 were at early stages of cirrhosis and none of them exhibited left ventricular systolic dysfunction. Only three of them had diastolic cardiac dysfunction. Song et al., showed that the MPI prior to transjugular intrahepatic portosystemic shunt (TIPS) insertion was high in their cirrhotic patients whose baseline MELD scores were 22 and both pre-TIPS MPI and MELD scores were significantly associated with survival rate after TIPS [16].

Wang et al., found that left and right ventricular MPIs increased and left and right ventricular stroke volumes decreased in compensated and decompansated cirrhotic patients [10]. Cirrhotic patients have usually hyperdynamic circulation with increased stroke volumes and cardiac output. In that study, MPI measurement was performed by conventional pulse Doppler examination which might have some limitations. As the echocardiographic data was derived from at least two different cardiac cycles in the conventional method, it could be affected by heart rate variability. However, in PW-TDI one single cardiac cycle is sufficient for Doppler examination. Additionally, Wang et al., did not mention whether patients with alcohol dependance were included in their study or not. Alcoholic cardiomyopathy is different from cirrhotic cardiomyopathy with dilated ventricules and depressed cardiac function [2]. These methodological differences might be the reason of increased MPI in their cirrhotic patients. Similarly, Ashmawy et al., demonstrated that left ventricular ejection fraction decreased and MPI increased in their cirrhotic patients [15]. Unfortunately, they did not report any information about the etiology of cirrhosis in their patient groups. In children whose etiology of cirrhosis were different from alcohol, Amoozgar et al., found that only right ventricular MPI increased before and six months after liver transplantation [17] and Fattouh et al., showed that both left and right ventricular MPIs increased [14].

Nt-pro-BNP is a sensitive marker to detect left ventricular dysfunction and appears to be an important predictor of cardiac complications [3]. In our study, increased intraventricular volume might lead to increased ventricular wall stress and this could stimulate Nt-proBNP secretion from ventricular myocytes. Since, our patients had no past history of cardiovascular disease and alcohol abuse, the increase in Nt-proBNP levels in decompensated patients might be the result of developing diastolic dysfunction and myocardial stress caused by cirrhosis.

In our study, cirrhotic patients showed elevated plasma concentrations of Nt-proBNP which was positively correlated with MELD scores, increased QT duration, CO and right atrial area and negatively correlated with diastolic blood pressure.

In the literature, there was a significant increase in the BNP levels in cirrhotic patients and its levels correlated with the severity of liver disease, CTP score [4, 7-10, 23] and MELD score [27, 28]. Decompensated cirrhotic patients with portal hypertension, ascites, spontaneous bacterial peritonitis, variceal bleeding and hepatic encephalopathy had higher levels of BNP [4-8]. BNP levels were significantly associated with increased left atrial enlargement, left ventricular hypertrophy, cardiac diastolic [4, 5, 29] and systolic dysfunction [11, 26].

Hurst et al., found that mean Nt-proBNP levels were 60.8 ± 54.9 pg/ml and 55.4 ± 41.4 pg/ml in patients with mild and moderate liver fibrosis and a cutoff value of greater than 290 pg/ml was highly predictive of advanced left ventricular diastolic dysfunction [4]. Similarly, in our cirrhotic patients who were in the early stages of cirrhosis, mean Nt-proBNP levels were 63.92 ± 18.45pg/ml. Only 3 patients showed diastolic dysfunction; one patient (CTP A) had mild, one patient (CTP B) had moderate and one patient (CTP B) had severe diastolic dysfunction.

Nt-proBNP levels were found to be negatively related to diastolic blood pressure in this study. In cirrhotic patients low peripheral vascular resistance may lead to decreased blood pressure [1] and with the progression of the disease, while blood pressure decreases the level of Nt-proBNP increases. Similarly, Hurst et al., found a negative relation between blood pressure and Nt-proBNP levels which increased mainly due to LV diastolic dysfunction [4]. In addition, Henriksen et al., showed a negative correlation between mean arterial blood pressure and proBNP levels [23]. According to Wiese et al., low mean arterial pressure was the only predictor of poor survival in stable cirrhotic patients [24].

In contrast to our findings, no positive relation of proBNP levels to cardiac output was observed in the study conducted by Henriksen et al. [23]. As all patients in their study, had a history of alcohol abuse, it was again impossible to exclude the cardiodepressant toxic effects of alcohol on left ventricular function.

In our study, there was a positive correlation between QT interval and Nt-proBNP levels and QT interval duration was longer in decompensated patients. Similarly, Bernardi et al., showed that prevalence of prolonged QT interval increased as CTP score increased and QT interval prolongation was significantly related to the severity of the underlying liver disease and CTP score. Additionally, they demonstrated a correlation between QT interval duration and plasma norepinephrine levels, indicating that one reason of this electrophysiological abnormality might be the sympathetic overactivity [30]. In the literature other reasons of prolonged QT interval were plasma membrane changes, reduced β-adrenoceptor density of myocytes, cardiotoxic effects of bile salts and nitric oxide [31].

Nt-proBNP levels were found to be positively correlated also with RA area in our study. Zhang et al., found that in alcoholic cirrhotic patients RA maximal area and RA volume index were higher and both RA and RV functions deteriorated. Unfortunately, in that study the influence of alcohol on right heart functions could not be excluded [32]. Patients with increased RA pressure before and after transjugular intrahepatic portosystemic shunt (TIPS) had approximately twice the mortality of those with normal RA pressure [33]. In the study of Fattouh et al., cirrhotic children had dilated RV and their BNP levels were correlated with E/e' ratio of RV, indicating that right heart functions were even affected in cirrhotic children [14]. Right ventricular diastolic dysfunction rate was reported to be high in chronic liver diseases [34], explaining positive correlation between RA area and Nt-proBNP levels.

Here, we did not observe systolic dysfunction and increased MPI in nonalcoholic cirrhotic patients. However, we demonstrated that in early stages of cirrrhosis increased Nt –proBNP levels together with diastolic dysfunction were positively correlated with MELD score, QT duration, RA area, CO and were negatively corelated with diastolic blood pressure. It is possible that in the late stages of disease, systolic dysfunction may develop and MPI may increase but this would better be evaluated further in studies especially addressing nonalcoholic patients.

Compliance with the Ethical Standards

Ethical Approval: The study was approved by the Clinical Research Ethics Committee of Marmara University, School of Medicine, Istanbul (03 – 2006-0124), and informed written consent was obtained from all the participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Comparing the effects of different amounts of fluid treatments in addition to analgesia in patients admitted to the emergency department with renal colic: A randomized study

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ABSTRACT

Objective: There are a limited number of studies examining the effect of fluid administration for acute pain relief in patients with renal colic. We aim to evaluate whether intravenous fluid of different amounts will make a difference regarding pain, in patients who presented to the emergency department (ED) with flank pain.

Patients and Methods: This single-center, prospective, randomized clinical trial was performed at the ED of a university hospital. Subjects were randomly assigned to three groups. All received an intramuscular (IM) injection of 75 mg diclofenac sodium and 3 mg intravenous (IV) morphine. While group 1 did not receive extra treatment, group 2 received 100 cc /hr physiological serum (PS), and group 3 received 500 cc /hr PS. Pain was assessed by using the visual analogue scale (VAS) ruler for 6 hours.

Results: A total of 201 patients were included. Mean age was 36.16 ± 9.85. At 60 min mean VAS scores were 3.55 ± 1.24 in the first group, 4.42 ± 1.87 in the second group and 5.02 ± 1.92 in the third group. In the group fluid not given, pain decrease was faster than others. At 240 min mean VAS scores were similar in all groups.

Conclusion: This study indicates that IV fluids given to patients with renal colic pain was not effective in pain relief.

Keywords: Renal colic, Analgesia, Intravenous fluid, Urolithiasis, VAS

1. INTRODUCTION

Urinary system stone complaints appear as a common disease with a high incidence in developed countries. 8-15% of Europeans and North Americans have urolithiasis [1]. In recent years, an increase in the incidence of urinary tract stones has been detected in developed countries [2,3]. Since, symptoms of anorexia, nausea and vomiting are common, fluid supplementation, maintenance of IV physiological serum (PS) infusion therapy is generally administered to prevent dehydration and fluid loss in patients with renal colic. However, it is not known exactly how much fluid should be given to the patients, and what the effects are of the fluids administered for pain and stone passage.

There are a limited number of studies examining the effect of fluid administration on acute pain relief. In literature, there are only two prospective and randomized studies, which found that a high amount of fluid and diuretic therapy accelerate stone passage in cases of acute renal colic [4,5] .

Our primary aim is to investigate whether intravenous fluid therapy has a role in reducing acute pain in the first 6 hours of admission to the emergency department (ED). We also aimed to analyze the general demographic data, comorbidities, family history and daily water consumption of patients who were admitted to the ED with renal colic.

2. PATIENTS and METHODS

Study Design

This study was designed as a prospective, randomized, double-blind, double-dummy, placebo-controlled, single-dose, single-center study. Marmara University, School of Medicine, Ethics Committee approved the study (09.2019.870). CONSORT guidelines were followed. We adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained.

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Our study was conducted on patients who were admitted to Marmara University Pendik Training and Research Hospital, Istanbul. The population of the study consists of all patients who applied to ED with complaints of flank pain. All patients who admitted to ED with acute flank pain, located in the right or left flank under the ribs extending from the axillary line to the hip and which can be described as pain in the groin, were examined by ED physicians. Patients who were suspected as suffering from renal colic during their examinations, underwent abdominal tomography for diagnosis and differential diagnosis. All patients who were found to have opacities were diagnosed as having stones in the urinary tract and were included in the study.

Patients under the age of 18, pregnant women, those with the Glasgow Coma Scale (GCS) <15 and those who showed limited cooperation, had had no oral intake for 12 hours, had fever> 38.3 ° C and systolic blood pressure <90 mmHg, who had used analgesics or antipyretics for any reason in the last 2 days, who were diagnosed with kidney failure, congestive heart failure, or pyelonephritis detected at the stage of diagnosis, who had undergone urinary tract surgery, who had a known allergy to any of the study drugs; who gave incomplete information or voluntarily left the ED during the observation period, and those who did not consent to participate in the study were excluded.

Patients included in the study were randomized by the closed envelope method. The treatment of each patient admitted to the observation room was determined in line with the group to which the patient was randomized and the treatment was initiated by the nurse on duty. Randomization was done using the Randomizer.org program [6].

Procedures for Treatment of Groups

Patients were randomized as Group 1,2 and 3. All groups were administered intravenously 75 mg diclofenac sodium as a non-steroidal anti-inflammatory drug and 3 mg morphine as a narcotic analgesic at time T0. In the first group, fluid was not given to the patients in addition to analgesic, but a nurse closed the serum set dosiflow with a cardboard and administered it to the patients. The patients were informed that fluid therapy was performed using serum. Unlike the first group, Group 2 had 100 cc / hour 0.9 % NaCl solution as an infusion for 6 hours. Since, the intravenous fluid infusion given was sealed with a cardboard, the patients were prevented from seeing the fluid ingested. Unlike the other groups, Group 3 had 500 cc / hour 0.9 % NaCl solution given as an infusion for 6 hours. Also the intravenous fluid infusion given was covered with a cardboard, and the patient was prevented from seeing the fluid ingested. Appropriate dose of morphine IV (not exceeding 10 mg in total) was administered as rescue therapy, if necessary, to patients whose pain was not relieved and who still needed analgesics in all groups.

Analgesic administration time was determined as T0, and the serum for the patients was started at the same time.

Hemogram, kidney function tests and complete urinalysis were sent from the patients determined as study candidates.

Written informed consent was obtained from patients who were found to have urinary tract stones on abdominal tomography and their treatment was initiated. After pain relief treatment of the patients was started, a questionnaire was filled in by a research assistant.

Patients included in the study were followed up in the ED for 6 hours. During the follow-up, any complications or drug side effects were noted. The patients who completed the study were started on home analgesic treatment and were referred to the outpatient follow-up or to the ward, according to the guidelines.

Physicians who were blind to the study groups asked the patients about pain by visual analogue scale (VAS) which is a validated, subjective measure for acute and chronic pain. Scores were recorded by making a handwritten mark on a 10-cm line representing a continuum between "no pain" and "acute pain" charts at certain intervals starting from the treatment, at 0, 15, 45, 60, 90, 120, 150, 180 and 240 min.

Total research population was 272. Sixty-two patients were excluded from the study (39 patients because they had been previously operated for urinary tract stones, 9 patients were diagnosed as having pyelonephritis, and 14 patients did not consent to the study). 210 patients were randomized. After randomization, 9 patients could not be included in the analysis due to missing data, so the data of 201 patients were analyzed. Flow chart is as Figure 1.

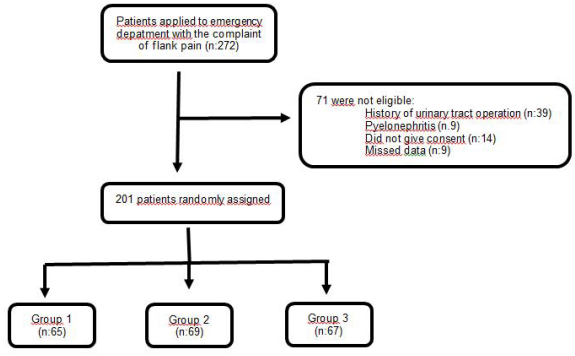

Figure 1. *Study flow chart*

Calculating the Sample Size

The sample size was calculated as 58 patients for each group in which the VAS score difference of at least 1 cm between at least two of the groups at any time could be detected, as the within-group standard deviation is 2 cm, but the type 1 error is 5% and the power is 80%. It was decided to recruit 20% more patients for each group, and at the end of the study, the groups were completed as 67, 69 and 65 patients. After the study was concluded, the power to detect the difference between the 3 averages of the study at 1 hour of treatment was determined to be 99%. In the whole study, type 1 error was accepted as 5%.

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Statistical Analysis

Continuous variables are given their mean and standard deviations and 95% confidence intervals, and the frequencies and percentages of categorical variables are given. Comparisons of continuous variables between groups were made with analysis of variance, and comparisons of categorical variables between groups were made with Fischer's exact test. The difference between the percentages of the categorical variables between the groups and the confidence intervals of this difference were also calculated and the effects were reported. The variation between consecutive measurements of VAS scores and whether there is a difference between these changes between groups was evaluated by analysis of the variance of consecutive measurements. P-value less than 0.001 was evaluated as statistically significant.

Before the study, the online sample size calculation program StatsToDo was used for sample size and post-hoc power calculation (https://www.statstodo.com/SSizAOV_Pgm.php).

All other analyses and graph breakdowns were calculated using Medcalc version 15.11.4 (Medcalc, Belgium).

3. RESULTS

Mean age of all 201 patients was 36.16 ± 9.85 (95% GA 34.79 – 37.53) and 171 (85.10%) of those were male. Among those who enrolled in the study, 60 (29.90%) patients had a history of nephrolithiasis, while 64 (31.80%) had a positive family history for it. Considering the water consumption of patients, 51 (25.40%) of them drank 5 to 6 glasses of water, 97 (48.30%) drank 7 to10 glasses and 53 (26.40%) drank over 10 glasses a day. As shown in Table I, the basic demographics and past medical and family histories of patients were similar in each group except for those with a history of diabetes.

Table I. *Distribution of patients according to demographics and comorbid diseases*

Demographics		Group 1 (n=67)	Group 2 (n=69)	Group 3 (n=65)	p
Age (year) mean ± SD (95% CI)		37.20 ± 10.60 (34.60 – 39.80)	36.30 ± 10.40 (33.80 – 38.80)	35.00 ± 8.40 (32.90 – 37.00)	0.42
Sex (male) n(%)		61 (91.00)	55 (79.70)	55 (84.60)	0.17
History of nephrolithiasis (+) n (%)		22 (32.80)	21 (30.40)	17 (26.20)	0.69
Water consumption (glass/day) n (%)	**5-6**	18 (26.90)	14 (20.30)	19 (29.20)	0.62
	7-10	29 (43.30)	36 (52.20)	32 (49.20)	
	>10	20 (29.90)	19 (27.50)	14 (21.50)	
Family history for nephrolithiasis (+) n (%)		17 (25.40)	24 (34.80)	23 (35.40)	0.37
History of DM n (%)		2 (3.00)	7 (10.10)	1 (1.50)	**0.04**
History of HT n (%)		7 (10.40)	9 (13.00)	2 (3.10)	0.11
History of CAD n (%)		3 (4.50)	4 (5.80)	1 (1.50)	0.43

DM: diabetes mellitus, HT: hypertention, CAD: coronary artery disease, SD: standard deviation, CI: confidence interval. p < 0.05 is statistically significant.

According to the computed tomography (CT) findings in the patients, concurrent hydronephrosis was detected in 177 (77.10%) and mean diameter of calculus was 5.83 ± 3.79 mm (95% GA 5.30 – 6.36). Calculi were located in the renal pelvis in 45 (22.40%) patients, in the ureters in 105(52.20%) patients, in the ureterovesical junction in 34 (16.90%) patients and in the bladder in 17 (8.50%) patients. There was no statistically significant difference between groups regarding the presence of hydronephrosis, size and location of calculi (Table II).

Table II. *Distribution of patients according to CT findings*

CT finding		Group 1 (n=67)	Group 2 (n=69)	Group 3 (n=65)	p
Diameter of calculus (mm) mean ± SD (95% CI)		5.90± 2.90 (5.20– 6.60)	6.30 ± 4.40 (5.20 – 7.40)	5.30 ± 3.90 (4.30 – 6.30)	0.32
Hydronephrosis n (%)		50 (74.60)	51 (73.90)	54 (83.10)	0.38
Location of calculus n (%)	Renal pelvis	16 (23.90)	18 (26.10)	11 (16.90)	0.80
	Ureters	32 (47.80)	37 (53.60)	36 (55.40)	
	Ureterovesical junction	12 (17.90)	10 (14.50)	12 (18.50)	
	Bladder	7 (10.40)	4 (5.80)	6 (9.20)	

SD: standard deviation, CI: confidence interval. p < 0.05 is statistically significant.

Intravenous morphine treatment was applied as rescue treatment to 18 of 67 (26.90%) patients in Group 1, 38 of 69 (55.10%) patients in Group 2 and 51 of 65 (78.50%) patients in Group 3. More rescue treatment was needed in Group 3, who were given the most vigorous fluid resuscitation, and the least in Group 1 who were not given any IV fluid. The difference between groups was statistically significant (p<0.01).

Table III. *Comparison of VAS scores in groups*

Time	VAS score (mm) mean ± SD (95%CI)			p
	Group 1 (n=67)	Group 2 (n=69)	Group 3 (n=65)	
min 0	7.73 ± 0.65 (7.56 – 7.89)	7.77 ± 0.67 (7.61 – 7.93)	7.97 ± 0.73 (7.80 – 8.14)	0.099
min 15	6.24 ± 1.15 (5.96 – 6.53)	6.41 ± 1.20 (6.12 – 6.87)	6.63 ± 1.18 (6.34 – 6.92)	0.183
min 45	5.11 ± 1.66 (4.75 – 5.46)	5.71 ± 1.64 (5.37 – 6.06)	5.80 ± 1.50 (5.45 – 6.16)	0.012
min 60	3.55 ± 1.24 (3.13 – 3.96)	4.42 ± 1.87 (4.02 – 4.83)	5.02 ± 1.92 (4.60 – 5.43)	**<0.001**
min 90	2.27 ± 1.35 (1.86 – 2.69)	3.23 ± 1.94 (2.82 – 3.64)	3.69 ± 1.80 (3.27 – 4.11)	**<0.001**
min 120	1.23 ± 1.15 (0.85 – 1.60)	2.09 ± 1.66 (1.72 – 2.46)	2.45 ± 1.78 (2.07 – 2.83)	**<0.001**
min 150	0.58 ± 0.84 (0.30 – 0.85)	1.07 ± 1.23 (0.80 – 1.34)	1.29 ± 1.27 (1.02 – 1.57)	0.010
min 180	0.24 ± 0.47 (0.08 – 0.41)	0.45 ± 0.72 (0.29 – 0.61)	0.58 ± 0.83 (0.42 – 0.75)	0.015
min 240	0.12 ± 0.33 (0.03 – 0.21)	0.10 ± 0.30 (0.02 – 0.19)	0.22 ± 0.45 (0.13 – 0.31)	0.157

Min: minute, SD: standard deviation, CI: confidence interval. p < 0.05 is statistically significant.

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In time, pain relief was seen in all groups. Considering mean VAS scores, there was no statistically significant difference between groups at time zero, 15 and 45 min. On the other hand, Group 1 had statististically significant lower mean VAS score at 60, 90 and 120 min. Statistically significant differences in VAS scores were not observed between groups either at 150, 180 or 240 minutes (Table III).

The decrease in consecutive VAS scores was significantly different both in groups and between groups ($p<0.001$; $p<0.001$ respectively).

Rescue treatment was not needed in a total of 93 (46 of 67 (73.10%) patients in Group 1, 31 of 69 (44.90%) patients in Group 2 and 14 of 65 (21.50%) patients in Group 3) patients. There was no statistically significant difference in mean VAS scores between groups ($p=0.21$).

None of the patients were discharged prior to 6 hours.

4. DISCUSSION

Renal colic is a common diagnosis in ED. In this study, we investigated the effect of the amount of fluid administered as acute pain treatment, using different amounts of intravenous fluid in addition to analgesic treatment for patients who were admitted to ED with flank pain and detected urinary system stones on their CT images. As a result of the study, we found that traditionally administered intravenous fluid did not help, and even the group receiving fluid needed more analgesic treatment.

The mean age of the patients included in the study was found to be 36.16 ± 9.85. In a study conducted in France and Germany, the most common age range for urinary stones was determined as 40-49 in men and 30-39 in women [7]. The average age value found in our study is compatible with the literature.

Of the patients in our study, 85.10% were men and the prevalence rate of kidney stones was higher than in many studies in favor of men. In many studies published abroad, it has been reported that there has been an increase in urinary system stone disease in women in recent years, and the rate of nephrolithiasis in men and women has decreased from 3: 1 to 1.30: 1 [8-11].

Almost half of the patients in our study stated that they consumed 1.5-2 liters of water a day, 25% consumed less than this. In a study reporting that when 2.5 liters of urine output is achieved due to a daily intake of more than 2 liters of water, it reduces the recurrence of kidney stones [12]. In our study, 75% of the patients consumed less than 2 liters of water.

Family history was positive in 31.80% patients. Most frequently, 47.60% patients had relatives other than mother, father and sibling; Subsequently, 31.70% patients had a history of stones in the father and 7.90% patients in the sibling. Although, there is a familial predisposition in urinary system stone disease, the relevant genes are not yet known [13].

Stone size in the CT images was evaluated and the average stone diameter was found to be 5.83 ± 3.79. In the study conducted by Edna et al., in Norway, the average stone size was found to be 4 mm, and 3.40 mm in the study of Springhart et al. [4,14].

In our study, the most common area where stones were detected was the ureter. Stones were detected in the ureteropelvic junction (UPJ) in 22.40% patients, in the ureterovesical junction (UVJ) in 16.90% patients, and in the bladder in 8.50% patients. In a study, the most common place where the stones were found was the UVJ and the proximal ureter [15]. In our study, the results were similar due to anatomical reasons.

When hydronephrosis occurs due to an acute cause, it does not remain asymptomatic as it is when due to a chronic cause, but creates colic-style pain. In various studies, the rate of hydronephrosis in urinary system stones has been reported as 69-83 % [16,17]. The rates of patients with hydronephrosis in our study are similar to those stated in the sources. Based on this data, it can be assumed that most of the patients included in our study had obstruction.

Due to the intense pain in renal colic, analgesics are used in the treatment. General practice in EDs is to give IV therapy in addition to analgesic therapy. Theoretically, it is thought that the IV fluid given will increase the hydrostatic pressure in the ureter, allowing the stone to move rapidly in the ureter, and the patient's pain will be relieved faster as a result of the quicker reduction of the stone. However, there are no clear recommendations in the guidelines regarding the effect of fluid administration on pain in patients and how much fluid should be given to patients. The number of studies conducted to investigate the effect of fluid treatments administered for acute pain attacks caused by kidney stones is limited. There are two prominent prospective and randomized studies on this subject. The first study highlighted in the Cochrane database is the work of Edna et al., in 1983 [4]. In this study, 60 patients were randomized to groups A and B; liquid was not given to group A for 6 hours, and 3 liters fluid infusion was given to group B. Pethidine was used as an analgesic. There was no difference between the groups in terms of pain and surgical intervention rates at the end of 6 hours, which were the endpoints. As a result of this study, it was found that IV fluid was not beneficial in renal colic pain. The second randomized controlled study emphasized in the Cochrane database was conducted in 2006 by Springhart et al., to investigate the effect of IV fluid administered in acute pain treatment of renal colic, 43 patients were enrolled in the study; patients in the first group, received 4 lt in 4 hours normal saline infusion, and those in the second group received 20 cc/ hour saline infusion [15]. Ketorolac and morphine were administered as an analgesic. In this study, no significant difference was found between the groups in terms of stone passage, additional medication need and hourly pain. The regression in the pain levels of the patients was similar in the groups with and without fluid. The results of these limited number of studies investigating the effect of IV fluid on pain in renal colic pain were in line with the results of our study. Also we found that even the group receiving fluid needed more analgesic treatment.

In our study, a faster pain response was detected in the mean VAS value of the first group, the group in which we did not give fluid, starting at 60 min and continuing at 90 and 120 min compared to the 2nd and 3rd groups in which we gave fluid. The group in which VAS averages were the highest during these time

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intervals, that is, the group in which the pain persisted, was the third group that received the most fluid. At 240 min mean VAS scores were similar between groups.

The reason for the delayed analgesic responses of the patients taking fluid may be that the administered fluid increased the volume of distribution by causing dilution in the applied analgesic doses. The significant difference between the VAS average values of the groups started to decrease from the 150th min and the difference disappeared at the 240th min, which was the ending point. At the end of the follow-up period, the level of pain in the groups with and without intravenous fluids questioned the efficacy of the fluid therapy routinely applied to most renal colic patients in many centers.

Considering the analgesics administered, morphine, which was given as rescue therapy to patients whose pain relief could not be obtained sufficiently, creates a significant statistical difference between the groups. The fact that the least need for rescue therapy was in Group 1 with 26.90% patients, who were also not given fluids, shows that fluid therapy increases the need for additional analgesics. One of the reasons why the number of patients needing additional doses of analgesics is clearly higher in the groups that are given fluid may be that the increased intravascular volume causes increased urine flow rate, a dramatic increase in ureteral peristalsis, which may possibly cause stone pushing. In this system, which has been obstructed due to the stone, the increase in pressure and tension caused by the IV fluid may cause an increase in the patient's pain. Another reason may be the accumulation of urine at a high urine flow rate and the fact that urine transport occurs according to the pressure gradient in the open tube [18,19].

As a result of our study, it was found that pain in renal colic patients with and without fluid therapy regressed to the same level at the end of the follow-up of the patients, and the need for additional medication in the group with fluid was higher than in the group without fluid. Further large-scale studies in which the patients enrolled in the study are evaluated in more detail are required to determine the effect and benefit on their functions,

There are limitations to this study. Patients admitted to ED with flank pain and who were diagnosed with urolithiasis as a result of their examinations were included in our study. This does not mirror the general population. Also, in our study, patients whose underlying heart failure would pose a risk to fluid administration were excluded Therefore, the data of these patients are lacking.

Before starting the study, although all physicians working in the ED received training for the research, and the differential diagnosis and diagnosis algorithm were explained, the fact that different physicians examined the patients may have created a bias in patient selection. Since, our study was conducted within the boundaries of the ED, some data may be said to be missing.

We conclude that IV fluids given to patients with renal colic pain was not effective in pain relief.

Compliance with Ethical Standards

Ethical Approval: This study was approved by the Ethics Committee of Marmara University, School of Medicine (09.2019.870). We adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained.

Financial Support: No specific funding was received.

Conflict of Interest: There are no conflicting interests.

Author contributions: LC, CO, OO and ES: Conceived the study and designed the trial, LC, CO, HA and AD: Supervised the conduct of the trial and data collection, LC: Undertook recruitment of participating patients and managed the data, including quality control, CO, ES and HA: Provided statistical advice on the study design and analyzed the data, OO: Chaired the data oversight committee, LC, CO, OO,ES, AD and HA: Drafted the article, and all authors contributed substantially to its revision, CO: Takes responsibility for the paper as a whole.

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Original Article

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Are histomorphologic changes in the fimbrial ends more to blame for primary epithelial ovarian carcinomas than initially thought?

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ABSTRACT

Objective: To investigate the relationship between primary epithelial ovarian tumors and histomorphologic changes in the fimbrial ends (FEs) of the fallopian tubes.

Materials and Methods: Twenty-eight serous carcinomas (SCs) and 12 non-serous carcinomas (NSC) were studied. Ovarian and concomitant invasive tumors in FEs were labeled with PAX8, WT-1 and Calretinin.

Results: Eighty-six percent of SCs were high grade (HG), 14% of were low grade (LG). 71% of SCs (85% HG, 15% LG) had concomitant invasive tumors in FEs. Serous tubal intraepithelial carcinoma (STIC) was seen in 29% (75% HG, 25% LG), all had concomitant invasive tumors in FEs. The presence of tumors in FEs was statistically significant in SCs (p=0.03). 33% of NSCs had concomitantly invasive tumors in FEs. 67% of endometrioid tumors, 33% of clear cell carcinomas had endometriosis. 50% of mucinous tumors, 67% of endometrioid tumors, 50% of benign Brenner tumors had Walthard nest. Except for mucinous carcinomas, ovarian and concomitant invasive tumors in FEs displayed tubal phenotype (Calretinin-/PAX8+).

Conclusion: The results of our study suggest that, invasive tumors and STIC in FEs are not only limited to HGSCs, but can also be seen in LGs. FEs could also be a site of origin for NSCs, however, future studies with more cases are needed.

Keywords: Primary epithelial ovarian tumors, Fallopian tubes, Fimbrial ends, Histomorphologic changes, Early detection

1. INTRODUCTION

Epithelial ovarian cancer constitutes the second most common gynecological malignancy with highest mortality in women [1, 2]. The high mortality rate is primarily due to the difficulties in diagnosis, including the lack of specific and sensitive biomarkers that could aid early diagnosis. Studies have shown that epithelial ovarian cancer is not a single disease, but it is composed of a diverse group of tumors that can be classified based on different morphologic and molecular features [3-5]. One group of tumors, designated type 1, is composed of low-grade serous carcinomas (LGSCs), low-grade endometrioid, clear cell, mucinous and transitional cell carcinomas [6, 7]. Another group of tumors, designated type 2, is highly agressive and includes conventional high-grade serous carcinomas (HGSCs), undifferentiated carcinomas and malignant mixed mesodermal tumors [3]. The most common subtype of ovarian carcinoma is serous carcinomas, and HGSCs comprise the vast majority. Thus, most of the studies have focused on HGSCs, and LGSCs have not been well-studied. LGSC is a unique entity with clinical and molecular characteristics distinct from HGSCs. Compared to HGSCs, LGSCs tend to occur in younger women, have indolent behavior and are chemoresistant [8]. In the last decade, studies have shown that HGSCs are likely derived from the epithelium of fimbrial ends (FEs). In contrast to HGSCs, it was assumed that, LGSCs arose from ovarian epithelial inclusions, serous cystadenoma or adenofibroma, and then progressed to serous borderline tumors and invasive carcinoma [9-13]. However, a few recent studies explored some histomorphological changes in the FEs of fallopian tubes, and concluded that secretory cells in fallopian tubes could be the source of LGSCs [14-16].

The aim of our study is to determine histomorphological findings (metaplasia, epithelial atypia, serous tubal intraepithelial

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carcinoma (STIC), invasive tumor), and evaluate any relationship between histologic types of ovarian carcinomas and these changes by using Senctioning and Extensively Examining the Fimbriated End (SEE-FIM) protocol for sampling fallopian tubes in groups with tumours and in control groups.

2. MATERIALS and METHODS

Our project was reviewed in 2012, and ethical approval was obtained from the Marmara University, School of Medicine Clinical Research Ethics Committee (approval number: 09.20120170).

Forty primary epithelial ovarian carcinomas between January 2011 and May 2014 were retrieved from the files. Cases with tumors that directly invaded the FEs were excluded from the study. Forty cases with tissue diagnosis of leiomyoma within the same period were included as the control group.

Serous carcinomas were graded according to M.D. Anderson criteria [17]. Tumor cells consist of uniform, round to oval nucleus with distinct nucleoli, mild to moderate nuclear atypia, and the mitotic index of up to 12 mitoses per 10 high power fields were classified as low-grade, while tumor cells with distinct pleomorphism, severe nuclear atypia, nucleus with coarsed chromatin pattern and mitotic index of more than 12 mitoses per high power were filed as high-grade [17]. Then, according to the p53 staining pattern, cases were reclassified as low or high grade.

Fimbrial ends of 80 cases (40 from tumor group and 40 from control group) were firstly evaluated by hematoxylin and eosin stain, to see if there were any histomorphological findings which replaced the normal tubal epithelium. Suspicious foci were reevaluated with serial tissue sections. Stratification with epithelial atypia, loss of cilia, hyperchromasia, presence of nucleolus, increased nucleocytoplasmic ratio and loss of polarity were considered significant for STIC.

Sectioning and Extensively Examining the Fimbriated End protocol was used for sampling fallopian tubes of all cases including the control group [18-20]. The best representative formalin-fixed paraffin-embedded tissue section (for tumor group; ovarian tumor and concomitant invasive tumor in FEs, for control group; normal appearing FEs) was chosen in each case. Three micrometer thickness sections were obtained and underwent overnight deparaffinization at 37°C. The sections were submerged for antigen retrieval in citrate buffer (ph 6.0). Immunohistochemical staining was performed with streptavidine biotin peroxidase method by using antibodies as follows: Calretinin (1:50, 5A5, Novocastra, Leica Biosystems, UK), PAX8 (1:200, MRQ50, Cell Marque, California, US), WT-1 (1:200, 6F-H2, Cell Marque, California, US) and p53 (1:800, DO7; Novocastra, Leica Biosystems, UK). Nuclear labeling in at least 25% of cells was considered to be expression for PAX8 and WT-1, and cytoplasmic for Calretinin. p53 was applied to FEs of both the tumor group and the control group. Regardless of presence of atypia, diffuse linear nuclear staining of equal to or more than 12 epithelial cells was considered significant for p53 signature.

Statistical Analysis

Fisher`s exact test was used for statistical analysis, and p values of <0.05 were considered statistically significant.

3. RESULTS

Distrubution of tumor types was summarized in Table I. Twenty eight (70%) cases were serous carcinomas (SCs), and 12 (30%) were non-serous carcinomas (NSCs). Median age in the tumor and control group was 56.2 years and 50.4 years respectively.

Serous carcinomas

Twenty four (86%) were HGSCs and 4 (14%) were LGSCs. Median ages of HGSCs and LGSCs 59 years and 56.5 years respectively. Concomitant invasive tumors were seen in FEs of 20 SCs (71%); 17 (85%) were HGSCs and 3 (15%) were LGSCs (Figure 1). STIC was seen in eight (29%) cases; six were (75%) HGSCs, two (25%) were LGSCs (Figure 2A), and all had concomitant invasive tumors in FEs (Figure 2B). There was no statistically significant difference between tumor grade and STIC or presence of invasive tumors in FEs (p=0.29 and p=0.68). However, the presence of concomitant invasive tumors in FEs was statistically significant in SCs, compared to NSCs (p=0.03) (Table II).

Table I. *Distribution of tumor types*

Histologic tumor type	Number of cases n (%)
Serous carcinoma	28 (70)
Mucinous tumor	4 (10)
Clear cell carcinoma	3 (7.5)
Endometrioid tumor	3 (7.5)
Brenner tumor	2 (5)
Total number of cases	40

Table II. *Comparison of the presence of tumors at the fimbrial ends between serous and non-serous carcinomas*

Histologic tumor type (n)	The presence of tumor at the fimbrial end n (%)
Serous carcinoma (28)	20 (71.4)
High grade serous carcinoma (24)	17 (85)
Low grade serous carcinoma (4)	3 (15)
Non-serous carcinoma (12)	4 (33)
Mucinous tumor (4)	0
Clear cell carcinoma (3)	1 (25)
Endometrioid tumor (3)	2 (50)
Brenner tumor (2)	1 (25)

p=0.03

p53 signature was seen in 11 (39%) cases (Figure 3A); eight (73%) had concomitant invasive tumor in FEs (Figure 3B), and three (27%) had STIC (Figure 3C). The presence of p53 signature and tumor grade was not significantly associated (p=0.48).

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All SCs were positive for PAX-8 (Figure 4A), 24 (86%) were positive for p53 (Figure 4B), and 24 (86%) were positive for WT-1 (Figure 4C). Calretinin was also positive in five (18%) cases (Figure 4D), and three (60%) of them were high-grade (Table III). The ovarian tumors and invasive tumors in FEs displayed tubal phenotype (Calretinin-\PAX8+) in 18 (90%) cases.

Table III. *Staining pattern of ovarian tumors in all cases*

Histologic tumor type (n)	p53 n (%)	PAX8 n (%)	WT-1 n (%)	Calretinin n (%)
Serous carcinoma (28)	24 (86)	28 (100)	24 (86)	5 (18)
Mucinous tumor (4)	0	0	0	0
Clear cell carcinoma (3)	1 (33)	1 (33)	1 (33)	0
Endometrioid tumor (3)	0	2 (67)	2 (67)	1 (33)
Brenner tumor (2)	1 (50)	0	1 (50)	0

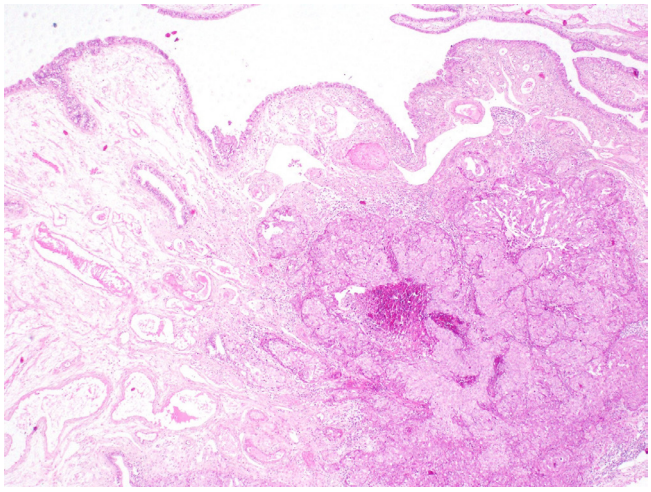

Figure 1. *Presence of tumor in the fimbrial end in serous carcinoma (H&E, X40)*

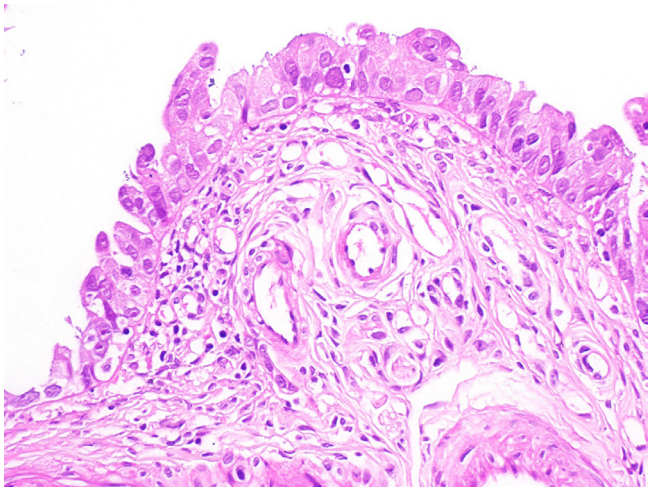

Figure 2A. *Presence of STIC in serous carcinomas (H&E, X200)*

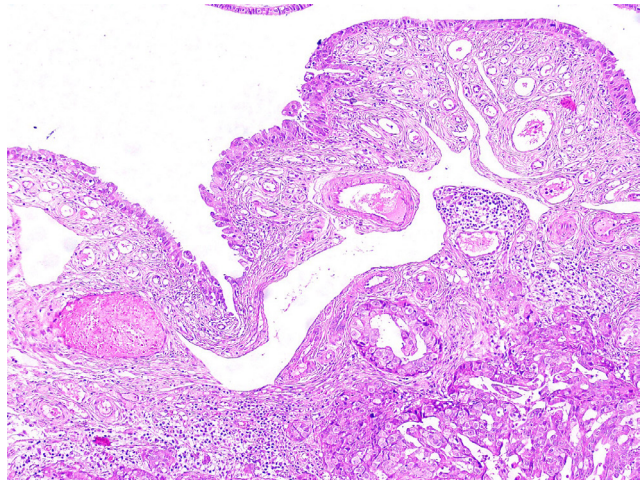

Figure 2B. *Presence of STIC and concomitant invasive tumor in the fimbrial end (H&E, X100)*

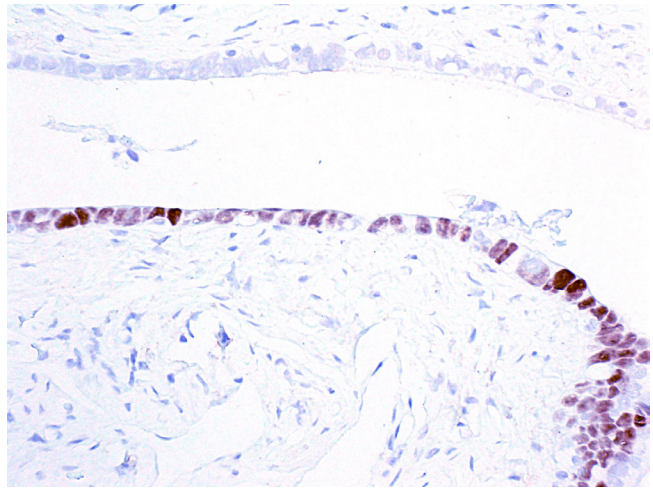

Figure 3A. *p53 signature (X200)*

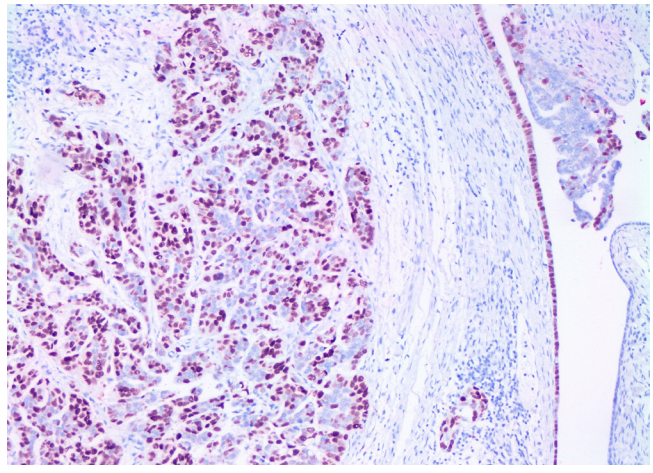

Figure 3B. *p53 signature and concomitant invasive tumor in the fimbrial end (X100)*

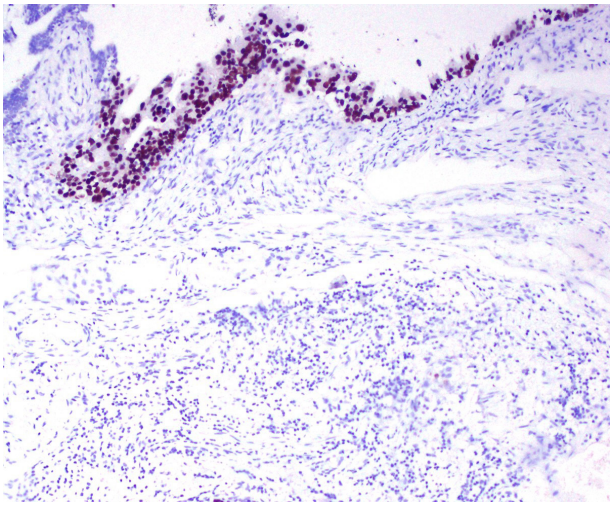

Figure 3C. *Presence of STIC and p53 expression (X100)*

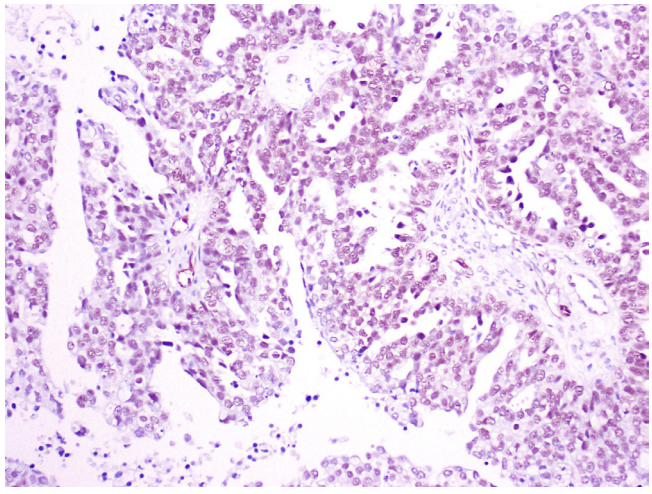

Figure 4C. *Expression of serous carcinomas for WT-1 (X200)*

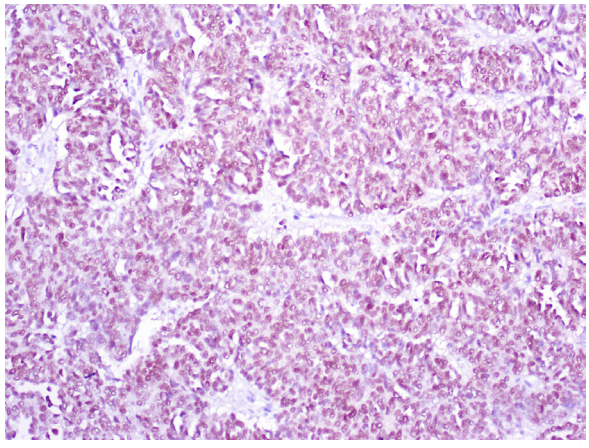

Figure 4A. *Expression of serous carcinomas for PAX-8 (X100*

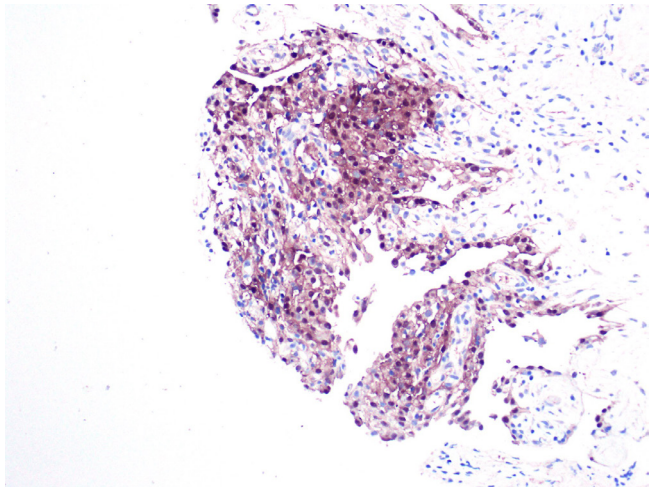

Figure 4D. *Expression of serous carcinomas for Calretinin (X200)*

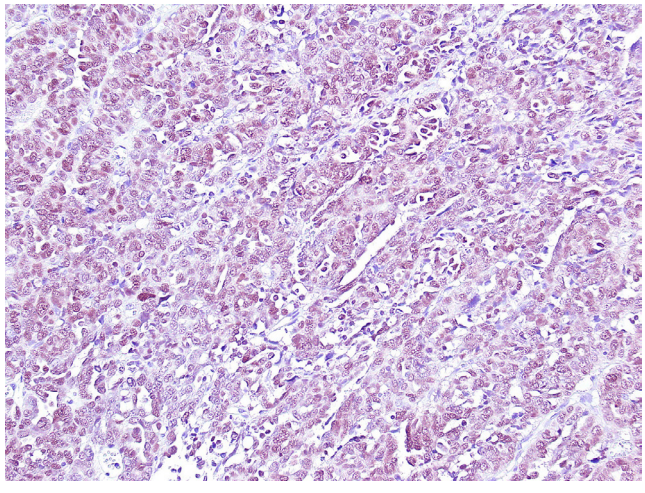

Figure 4B. *Expression of serous carcinomas for p53 (X100)*

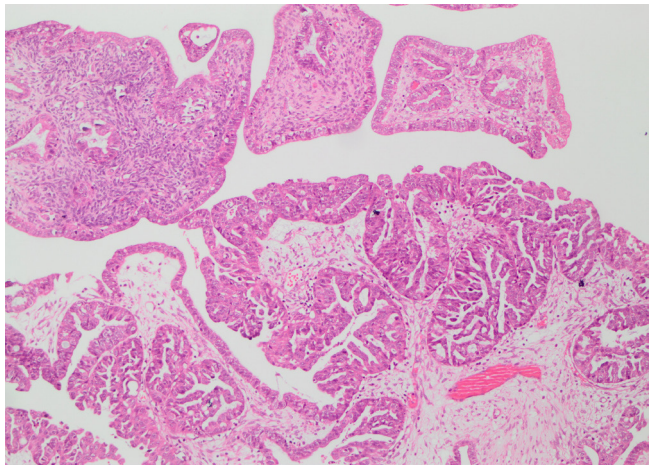

Figure 5A. *Endometrioid tumor (H&E, X100)*

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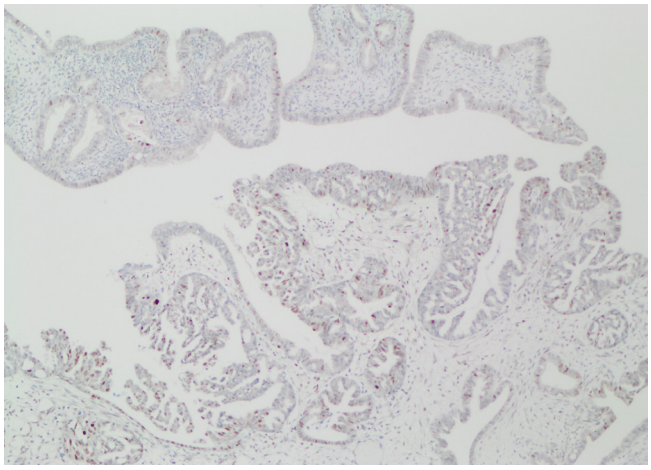

Figure 5B. *Expression of endometrioid tumor for p53 (H&E, X100)*

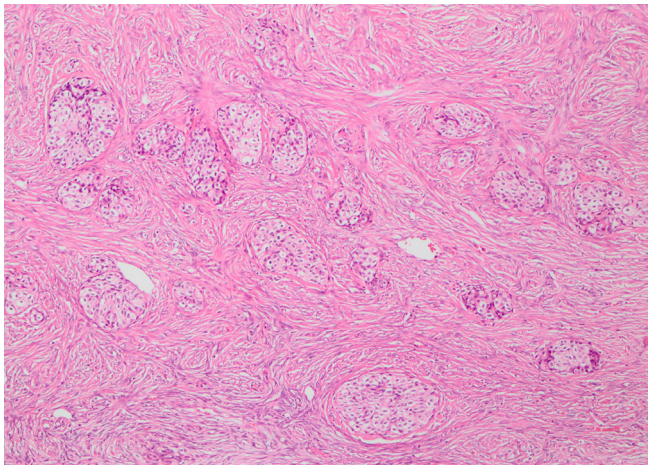

Figure 6A. *Brenner tumor (H&E, X100)*

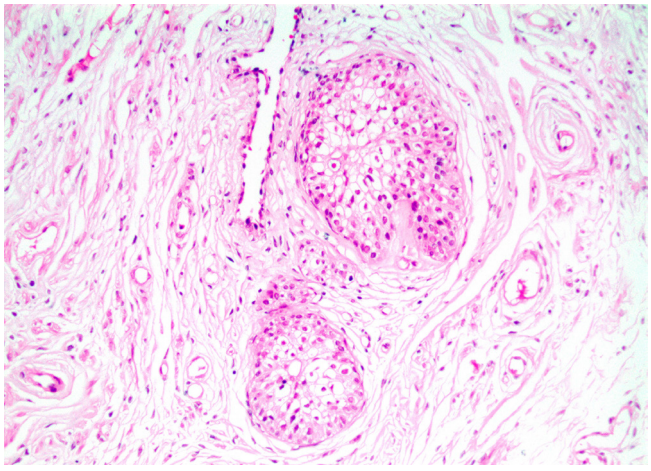

Figure 6B. *Brenner tumor and concomitant invasive tumor in the fimbrial end (H&E, X200)*

Non-serous carcinomas

A total of 12 cases were NSCs including four (33%) mucinous tumors, three (25%) clear cell carcinomas, three (25%) endometrioid tumors and two (17%) benign Brenner tumors. Three (75%) mucinous tumors and two (67%) endometrioid tumors were borderline. The concomitant invasive tumors in FEs were seen in four (33%) cases; two endometrioid tumors (Figure 5A and 5B), one clear cell carcinoma and one benign Brenner tumor (Figure 6A). No invasive tumor or TIC was seen in the FEs of mucinous tumors. Although, this ratio is less than in SCs, more studies with a larger number of cases should be carried out for equitable comparison. One (8%) case had TIC, and five (42%) had p53 signature. There was no statistically significant difference in presence of p53 signature between SCs and NSCs (p=0.58) (Table IV). Endometrioid tumors (67%) which had invasive tumors in FEs, had also endometriosis foci in FEs. No in situ carcinoma was seen in FEs and one had p53 signature. The clear cell carcinoma case which had invasive tumor in FEs, had also TIC and endometriosis foci. The benign Brenner tumor case which had invasive tumors in FEs (Figure 6B) had also p53 signature and Walthard nest in FEs. Walthard nest was also seen in 50% of mucinous tumors and 67% of endometrioid tumors. Except mucinous tumors, ovarian tumors and concomitant invasive tumors in the FEs displayed tubal phenotype (Calretinin-\PAX8+) in all cases.

Table IV. *Comparison of p53 signature between serous carcinomas and non-serous carcinomas*

Group (n)	p53 signature n (%)
Serous carcinomas (28)	11 (39)
Non-serous tumors (12)	5 (42)
Total number of case (40)	16

p=0.58

Table V. *Comparison of the presence of tumors at the fimbrial end in the literature and in our study*

The name of the study	Tumor at the fimbrial end (%)
Mehra et al 2011 [19]	80
Medeiros et al 2006 [18]	38
Salvador et al 2009 [20]	58
Our study	71

4. DISCUSSION

The current study is one of the few studies investigating the fallopian tubal epithelial pathologies in SCs graded by M.D Anderson criteria. The incidence of invasive tumor in the FEs of HGSCs (85%) is significantly higher than in LGSC (15%). As a result, we found that FE could be the origin of not only the HGSCs but also the LGSCs.

Women with BRCA germ line mutations, who had undergone prophylactic salphingooophorectomy, were studied for targeted region of serous carcinogenesis in previous studies (Table V).

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While Mehra et al., found invasive tumors in FEs in 80% of the cases, Medeiros et al., identified invasive tumours in 38% of women with BRCA germ line mutations [20,21]. Salvador et al., studied sporadic SCs. They found invasive tumors in FEs in 58% of cases, and all were HGSCs [23]. These studies have provided evidence that the fallopian tube, especially the fimbria is the primary site of most HGSC. In our study, we found a high percentage (71%) of invasive tumors in FEs of SCs, and 85% of them were HG.

The origin of LGSC is less clear compared to HGSCs, as there were only few studies related to this tumor group [8, 12, 14, 15]. The few LGSC can be the main issue for this. Also, different grading systems among these studies prevent accurate comparison.

The theory that SCs originate from fallopian tubal epithelia was further supported by the presence of a high percentage (59%) of STIC accompanied with invasive tumors in HGSCs. However, LGSCs were not mentioned in these studies [24, 25]. In our study, the incidence of STIC was 21%, and invasive tumors in FEs of HGSCs and LGSCs were 85% and 15% respectively. [9, 21]. This showed that invasive tumors and STIC could be found in LGSCs as well as in HGSCs.

In literature, the association between p53 signature and STIC was reported in a wide range (20-60%) [26]. In our study, p53 signature was seen in 11 (39%) SCs; three (27%) had STIC, and eight (73%) had concomitant invasive tumor in FEs. This difference can be explained by different sampling methods of FEs, as in most of the studies no information was given about the sampling method. Presence of STIC or invasive tumor in FEs among all cases, where p53 signature was identified, gave rise to the opinion that HGSCs are originated from this sequence [9, 11]. We found that p53 signature could be identified independently from tumor grade and was not only specific for HGSCs, but also can be seen in LGSCs and NSCs.

The precursors of STIC, identified as p53 signature, was reported approximately 10-40% within normal population in literature. Most studies reported that the ratio of this incidence can be changed by studying with different ethnic groups and sampling methods. By sampling with SEE-FIM protocol, the incidence was found higher [19, 24], and in our study p53 signature was identified in six (15%) of control group which was compatible with literature.

In additon to histomorphologic features, performing immunohistochemical stains including PAX8, WT-1 and Calretinin, was suggested to determine the origin of tumor. It is thought that the tumor is originated from fallopian tubal epithelium, if it is positive for PAX8 and negative for Calretinin, while it is originated from mesothelium if stained vice versa [15, 25, 26]. In our study, ovarian tumor and concomitant invasive tumor in FEs showed tubal phenotype in 18 (90%) SCs. Five (18%) SCs were positive for Calretinin. The significant relationship with HGSCs and Calretinin positivity were reported in recent studies, and this was explained by loss of tumor differentiation. In our study, 60% of Calretinin positive carcinomas were high grade. In addition, it has also been proposed that, some ovarian tumors arise from the mesothelial surface lining of the ovaries or from invaginations of this lining into the superficial ovarian cortex that form cortical inclusion cysts. Thus, these inclusion cysts were blamed for precursor lesions of ovarian carcinomas [30]. However, to make an exact comment, we thought that histomorphological changes and staining pattern of ovarian inclusion cysts should also be studied.

A few studies about NSCs located in FE were reported. However, the fimbriae were not examined in detail in any of these cases. Alvarado-Cabrero et al., studied SCs and NSCs located in FE, but in this study, the survey was evaluated, instead of the histomorphological findings of the fimbriae [28]. Maeda et al., studied 52 primary ovarian carcinomas, and invasive tumors in FEs were only seen in SCs [29]. Seidmann et al., studied Brenner tumors, and no invasive tumor or precursor lesion was found in the FEs. However, Walthard nests were evident in 20% of cases. By detailed sampling of the FEs and examining the precursor lesions, comments about the origin of mucinous and Brenner tumors could also be made [30]. According to the results of these studies, it was thought that NSCs could also have originated from the FEs [31, 32]. In our study, concomitant invasive tumors in the FEs were seen in four (33%) NSCs; two (%50) were endometrioid tumors, one (%25) was clear cell carcinoma, and one (%25) was benign Brenner tumor. No concomitant invasive tumor in the FEs was seen in the mucinous tumors. Mucinous tumors were also different from other types of tumors by their staining pattern, since they displayed mesothelial phenotype (Calretinin+\PAX8-). The limitation of our study was too few cases for studying the relationship between NSCs and FEs. However, we thought that detailed sampling of FEs in all ovarian carcinomas was important for obtaining precursor lesions. Except for mucinous tumors, the relationship between FE and NSCs may be found by studying more cases.

Conclusion

Our findings suggest that most SCs, regardless of tumor grade, originate from FEs. Although, the number of cases is quite low, our study suggests that NSCs can also originate from FEs. To determine the relationship between NSCs and FEs, more cases should be studied with detailed sampling method. The results of all these studies are helpful for both classification of primary ovarian epithelial carcinomas and precursor lesions. Also, recognising the origin of precursor lesions could light the way for ideas on more conservative surgeries, which is vital for reproductive women.

Compliance with the Ethical Standards

Ethical Approval: The study protocol was approved by the Marmara University, Faculty of Medicine, Ethics Committee with the (approval number: 09.20120170).

The study was conducted in accordance with the principles of the Declaration of Helsinki.

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The relationship between abdominal obesity and irritable bowel syndrome in adults

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ABSTRACT

Objective: The aim of this study is to evaluate the relationship between irritable bowel syndrome (IBS) and abdominal obesity.

Patients and Methods: This is a cross-sectional study, consisting of 18-49 year old patients who applied to Marmara University School of Medicine's Family Medicine outpatient clinics and who accepted to participate. A questionnaire was applied using face-to-face interview technique; anthropometric measurements were obtained as recommended by World Health Organization (WHO). The diagnosis of IBS was made for those who fully met the diagnostic criteria of ROME IV-IBS and had no alarm symptoms. Abdominal obesity of the participants was determined via anthropometric measurements. Statistical analyses were performed by using SPSS 20 package program.

Results: A total of 487 patients participated in the study: 77% female, 33% male; mean age value 33.71±8.59 years. The prevalence of IBS was 24.2% (n=118) [F:27.2% (n=102), M:14.3% (n=16)]. Abdominal obesity prevalence was 31.2% (n=152) [F:24.5% (n=92, M:53.6% (n=60)]. There is no statistically significant difference in terms of abdominal obesity with and without IBS (p>0.05).

Conclusion: In this study no statistically significant relationship has been detected between IBS and abdominal obesity.

Keywords: Irritable bowel syndrome, Abdominal obesity, Central obesity

1. INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by chronic abdominal pain and variable bowel habits and which affects the patient's quality of life negatively. The causes of IBS still remain unclear [1]. The prevalence of IBS is reported as 7 to 45% in different countries [1,2]; in Turkey this rate varies between 6.2% and 33.5% [3,4]. IBS is more common and symptoms are more prominent in females [1,2,5]. IBS rarely begins after 60 years of age while its prevalence decreases after the fifties [1,2,6]. Although, the diagnosis can be easily made according to ROME IV criteria, the chronicity of the disease, and unrelieved and recurring symptoms cause patient dissatisfaction [1]. This leads to unnecessary consultations, unnecessary use of advanced diagnostic tests and medications, even interventions that lead to surgical operations which increase health expenditure and cause loss of labor [7]. Due to all these reasons and its high prevalence, IBS is one of the diseases that should be managed in primary care.

Abdominal obesity is also a global health problem, its prevalence is still increasing all over the world [8,9]. Intra-abdominal fat accumulation is known as the primarily responsible factor for increased mortality and morbidity, therefore, abdominal obesity is a significant indicator in terms of metabolic and cardiovascular risk factors [10,11]. The gold standard measurement methods of abdominal obesity are computerized tomography (CT), Dual-X-Ray and magnetic resonance imaging (MRI) [12,13]. These methods are not usable for primary care because of exposure to radiation, and furthermore they are expensive and difficult to access [14]. World Health Organization (WHO) recommends waist circumference as the cheapest, most accessible and closer result for determining abdominal obesity (≥104cm for males, ≥88cm for females) [10]. In recent years, the bioimpedance analysis (BIA) method which is based on the difference in lean tissue mass and the electrical permeability of adipose tissue has emerged as another safe, easily accessible and economical method to show abdominal obesity [15].

Some studies report an increasing risk of developing upper gastrointestinal system (GIS) symptoms in relation to increasing body mass index (BMI) [16-18], but the relationship between obesity and lower GIS symptomatology, especially IBS, remains unclear. Regarding the relationship between IBS and abdominal obesity, which is a commonly encountered clinical problem in

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obesity, the evidence is still limited; only Lee et al.'s study suggests a relation between abdominal obesity and diarrhea dominant IBS (IBS-D), which implicates the need for more clinical studies [19].

The aim of this study is to evaluate the relationship between IBS and abdominal obesity.

2. PATIENTS and METHODS

Study Type

This is a cross-sectional study. The sample size has been calculated as 470 participants based on a confidence level of 95%, acceptable error 3%, and 13% IBS prevalence which was accepted as the average percentage according to the other studies' results in the literature [1-4].

The Universe of the Study and Recruitment of the participants

The 18-49 years old patients who applied to the Marmara University Pendik Training and Research Hospital Tuzla and Maltepe Education Family Health Centers and University Family Medicine outpatient clinics with any complaint between October 2017 and February 2018, were accepted as the universe of the study. The patients were informed about the study by the researcher and by wall-posts. Interested patients were interviewed for inclusion criteria until the sample size was reached. A total of 487 patients were recruited for the study.

Inclusion and Exclusion Criteria for the Study

Inclusion criteria were: patients had to be between 18 and 49 years of age, as 50 and over 50 year olds counted as one of the alarm symptoms [20]; participation had to be voluntary, and there should be no communication barrier. Patients with a history of GIS diseases such as inflammatory bowel disease, lactose intolerance, colon cancer, celiac disease, gastrointestinal surgery; with diagnoses of psychiatric diseases such as schizophrenia, bipolar disorder; who were pregnant or having suspicion of pregnancy; who had mental and/or physical disabilities were excluded from the study. These disorders depended on the patients' own admissions.

Data Collection Process

Ethical approval was obtained from the Ethical Committee of Marmara University Clinical Studies dated 06.10.2017 with protocol no 09.2017.601 for the study entitled as "Relationship between abdominal obesity and irritable bowel syndrome in adults". All participants gave informed consent.

Data collection tools/ questionnaires utilized in this study were: 1. A questionnaire including sociodemographic information prepared by the researchers; 2. ROME IV-IBS diagnostic criteria, alarm symptoms [1,20]; 3. Bristol Stool Scale used to differentiate subgroups [1,20].

These questionnaires were applied to all of the participants using face to face interview technique by the researcher in outpatient clinics. Anthropometric measurements were: Height and waist circumference were measured according to the recommendations of the WHO, by the same researcher [10]. A constant-tension tape measure, a BIA device (Inbody 170, Seoul, Korea) and height meter were used for taking the measurements and BMI [weight (kg)/height (m^2)] was calculated.

Definition of abdominal obesity

Abdominal obesity is defined based on waist circumference measurements according to the recommendations of the WHO. Cut-off values for abdominal obesity were defined as ≥104cm for males, ≥88cm for females by WHO. However, WHO recommends the use of cut-off values of their country to researchers, obtained from large scaled studies performed in the country [10]. In our study waist circumference cut-off values of Turkey Diabetes, Hypertension, Obesity and Endocrinological Diseases Prevalence Study (TURDEP II), a nationwide study realized with the participation of 26.499 Turkish adult people, were taken into consideration (≥90cm for females, ≥96cm for males) [9]. The other abdominal obesity measurement method in our study was BIA which provides high accuracy for visceral adipose tissue [14]. BIA device estimates the participants' trunk fat deposition individually as 'lean', 'normal' and 'over'. The participants determined 'over' for trunk fat by BIA device were accepted as abdominal obese.

Definition of IBS

Irritable bowel syndrome is defined according to the ROME IV diagnostic criteria including subgroup determination (constipation, diarrhoea, mixed and unclassified based on Bristol Stool Scale [1,20]) and excluding alarm symptoms such as iron deficiency anemia, rectal bleeding, unintentional weight loss, fever, changing bowel habits [20].

ROME IV criteria for IBS were: Recurrent abdominal pain, on average, at least 1 day/week in the last 3 months, associated with 2 or more of the following criteria: 1. Related to defecation, 2. Associated with a change in frequency of stool, 3. Associated with a change in form (appearance) of stool. Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis [20].

Irritable bowel syndrome is classified into four subgroups. Predominant bowel habits are based on stool form on days with at least one abnormal bowel movement. According to Bristol Stool Scale, >25% type 1 or 2 stool form is accepted as constipation-predominant type (IBS-C), >25% type 6 or 7 stool form is accepted as diarrhoea-predominant type (IBS-D), >25% type 1 or 2 and >25% type 6 or 7 stool forms are accepted as mixed type with constipation and diarrhoea (**IBS-M**). The other subgroup is unclassified type (IBS-U)**.** This type complies with diagnostic criteria but does not meet other grouping standards [1].

Statistical Analysis

Statistical analysis was performed in SPSS version 20.0 for the Windows (IBM Corp.; Armonk, NY, USA) program. Frequency distribution, mean and median values of all independent variables were calculated; For comparisons between categorical variables Chi-Square test and t test for continuing versus categorical variables were used. The statistical significance threshold was accepted as p value under 0.05 should be considered as significant.

3. RESULTS

A total of 487 individuals participated in our study; 77% (s=375) female, 23% (n=112) male. The mean age of the participants was 33.7±8.6. Prevalence of IBS was determined as 24.2% (n=118); IBS subgroup prevalence was 39.8% (n=47) for IBS-C (constipation-predominant), 26.3% (n=31) for IBS-U (unclassified), 24.6% (n=29) for IBS-D (diarrhoea-predominant), 9.3% (n=11) for IBS-M (mixed type). Sociodemographic and health related characteristics of IBS and non-IBS groups and their comparative analysis results are summarized in Table I. There was a statistically significant difference between the two groups only in terms of gender and fibromyalgia. IBS was more prevalent in females; fibromyalgia was more prevalent in participants with IBS (p=0.003, p=0.033, respectively).

Table I. *Sociodemographic and health related characteristics and comparison between groups of participants with and without IBS*

Characteristics		IBS(+)		IBS(-)		Total		
		n	%	n	%	n	%	p*
Gender								
Female		102	27.2	273	72.8	375	100.0	0.003
Male		16	14.3	96	85.7	112	100.0	
Age groups								
18-24 years		18	19.6	74	80.4	92	100.0	0.674
25-34 years		47	27.5	124	72.5	171	100.0	
35-49 years		53	23.7	171	76.3	224	100.0	
Marital status								
Married		83	25.9	238	74.1	321	100.0	0.146
Single		35	21.1	131	78.9	166	100.0	
Education								
Secondary school and below		28	21.2	104	78.8	132	100.0	0.204
High school and above		90	25.4	265	74.6	355	100.0	
Employment								
Employed		75	24.8	227	75.2	302	100.0	0.388
Unemployed		43	23.2	142	76.8	142	100.0	
Income status								
≤1404 TL		28	25.9	80	74.1	108	100.0	0.143
1404-4890 TL		78	25.8	224	74.2	302	100.0	
≥4891TL		12	15.6	65	84.4	77	100.0	
Medical history								
Hypertension		4	3.4	18	4.9	22	4.5	0.349
Diabetes		6	5.1	17	4.6	23	4.7	0.499
Cardiovascular diseases		3	2.5	14	3.8	17	3.5	0.377
Hypothyroidism		10	8.5	33	8.9	43	8.8	0.523
Depression		8	6.8	17	4.6	25	5.1	0.239
Upper GI diseases		22	18.6	54	14.6	76	15.6	0.183
Fibromyalgia		4	3.4	2	0.5	6	1.2	0.033
Smoking status	Never	66	55.9	230	62.3	296	60.8	0.346
	Former	19	16.1	43	11.7	62	12.7	
	Current	33	28.0	96	26.0	129	26.5	
Alcohol	Yes	15	12.7	46	12.5	61	12.5	0.527
	No	103	87.3	323	87.5	426	87.5	
Total		118	24.2	369	75.8	487	100.0	

**Chi-Squared test, p<0.05*

The abdominal obesity frequency in IBS and non-IBS participants and their comparative analysis according to TURDEP II, WHO cut-off values and BIA results are summarized in Table II.

Table II. *Abdominal obesity according to TURDEP II, WHO, BIA and their comparative analyses in IBS and non-IBS groups*

Abdominal Obesity for		IBS (+)		IBS (-)		Total		
		n	%	n	%	n	%	p*
TURDEP II	(+)	38	32.2	114	30.9	152	31.2	0.436
	(-)	80	67.8	255	69.1	335	68.8	
WHO	(+)	14	11.9	63	17.1	77	15.8	0.112
	(-)	104	88.1	306	82.9	410	84.2	
BIA	(+)	89	75.4	285	77.2	374	76.8	0.385
	(-)	29	24.5	84	22.8	113	23.2	
Total		118	100.0	369	100.0	487	100.0	

**Chi-squared test, p<0.05*

IBS: *Irritable bowel syndrome,* ***TURDEP II:*** *Turkey Diabetes, Hypertension, Obesity and Endocrinological Diseases Prevalence Study,* ***WHO:*** *World Health Organization,* ***BIA****: Bioimpedance analysis*

Participants with and without IBS were compared as to whether there was a difference in terms of mean waist circumference (cm). There was no statistically significant difference between the groups (p>0.05).

No statistically significant relationship was detected between IBS and IBS subgroups and GIS symptoms except constipation. The results are summarized in Table III.

Table III. *Comparison of IBS subgroups and GIS symptoms with abdominal obesity*

IBS subgroups and GIS symptoms	Abdominal obesity						
	(+)		(-)		Total		
	n	%	n	%	n	%	p*
IBS-C	17	63.8	30	36.2	47	100.0	0.290
IBS-D	10	65.5	19	34.5	29	100.0	0.465
IBS-M	1	9.1	10	90.9	11	100.0	0.076
IBS-U	10	32.3	21	67.7	31	100.0	0.581
Constipation	68	27.4	180	72.6	248	100.0	0.041
Diarrhoea	50	28.2	127	71.8	177	100.0	0.167
Nausea	52	29.1	127	70.9	179	100.0	0.248
Vomiting	18	25.7	52	74.3	70	100.0	0.176
Bloating	100	31.6	216	68.4	316	100.0	0.431
Pain during defecation	48	27.7	125	72.3	173	100.0	0.130

**Chi-Squared test, p<0.05*

IBS: *Irritable bowel syndrome,* ***GIS:*** *Gastrointestinal system,* ***IBS-C:*** *Irritable bowel syndrome with predominant constipation,* ***IBS-D****: Irritable bowel syndrome with predominat diarrhoea,* ***IBS-M****: Irritable bowel syndrome-mixed type,* ***IBS-C:*** *Irritable bowel syndrome-unclassified type*

4. DISCUSSION

According to the results of our study, no relationship between abdominal obesity and IBS was detected; there was no statistically significant difference between the IBS and IBS subgroups and non-IBS groups in terms of abdominal obesity.

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Lee et al., had reported that abdominal obesity was related to an increased risk of IBS in IBS-D subgroup [19]. In their study, abdominal obesity was measured by CT which was a part of the routine health control in this country. CT is accepted as a gold standard method for the diagnosis of abdominal obesity. However, as it is expensive, not easily accessible and because of exposure to radiation, it is not a preferred method for primary care patients [14]. The main difference between Lee et al.'s and our study may be due to the use of different diagnostic methods. WHO recommends the measurement of waist circumference as the cheapest, more accessible and closest to the ideal method to determine abdominal obesity [10]. In our study abdominal obesity is defined based on waist circumference measurement and the BIA; no statistically significant difference was detected between the IBS and IBS subgroups and non-IBS groups in terms of abdominal obesity, using both measurements.

Computerized tomography was also used in the clinical trial of Nagata et al., evaluating the relation between bowel symptoms and visceral fat tissue. It was determined that the risk of constipation and hard stools was related to low visceral adipose tissue (VAT) and low subcutaneous adipose tissue (SAT), which are criteria for abdominal fat deposition and equally mean abdominal obesity [21]. In our study, complaint of hard stools/constipation and/or being in IBS-C subgroup were not significantly related to the presence of abdominal obesity.

Prevalence of IBS was detected as 24.2% in our study**.** In a meta-analysis of 80 studies, the world-wide prevalence of IBS was reported as 11.2% (1% – 45%) [1]. In the studies performed in Turkey this prevalence varied from 6.3% to 33.5% [3,4]. As for the subgroups, in our study IBS-C was the most prevalent form similarly to the meta-analysis of Lovell et al. [2]. In our country, although, the prevalence of IBS subgroups differed among studies, IBS-C was the most commonly detected subgroup [3,4].

Based on clinical studies, IBS is related to several factors such as female gender, psychiatric disorders, fibromyalgia, GIS tract disorders [22,23]. There is evidence of the relation between abdominal obesity and factors such as female gender and upper GIS disorders [9,24]. In our study a comparison of IBS and non-IBS groups was made in terms of these factors.

Irritable bowel syndrome was significantly more prevalent in female participants (27.2%) than in males (14.3%) similar to the literature [5]. The prevalence of IBS was higher in participants with a higher educational level, but this difference was not statistically significant. According to the results of different studies, the relationship between IBS prevalence and education level is contradictory. In other studies from different countries, the results were similar or there was a linear relation between them [25]. In our country, the increased prevalence of IBS was reported in relation to lower education level [3].

According to the health characteristics of the participants, upper gastrointestinal diseases such as gastro-esophageal reflux disease, peptic ulcer and gastritis, diabetes and depression were more frequent in the IBS group, but this result was not statistically significant. Only fibromyalgia was significantly more prevalent in the IBS group, which is compatible with literature [23]. Concerning smoking status, however, IBS was more frequently detected among participants who never smoked, there was no statistical significance. IBS was more prevalent among participants who used alcohol, which was still not statistically significant. Reding et al., in their study examining the relation of alcohol use in IBS individuals with gastrointestinal symptoms, stated that the effect of alcohol use in IBS individuals on gastrointestinal symptoms is still unclear [26].

The strengths of the study; anthropometric measurements and questionnaire were applied by a single physician with a standard approach. It was performed using two different waist circumference cut-off values and the BIA method which supported both results.

The limitations of this study may be summarized in two items. Firstly, the history of their diseases and medication use was based on the patients' own revelations, not on laboratory results. Secondly, some health problems such as hypothyroidism, diabetes which can alter gastrointestinal functions, were not excluded from the study since this study was performed in primary care clinics where the patients are frequently multimorbid and they apply with an undifferentiated complaint so that it was difficult to find an isolated IBS patient.

In conclusion, the main outcome of the study was no statistically significant relationship between IBS and abdominal obesity. The social and health determinants related to IBS, female gender, depression and fibromyalgia were in significant relation with abdominal obesity which can be perceived as supporting the main result.

Compliance with the Ethical Standards

Ethical Approval: Ethical approval was obtained from the Ethical Committee of Marmara University Clinical Studies dated 06.10.2017 with protocol no 09.2017.601 All participant gave written informed consent.

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Author Contributions: YDK and AU: Conceived and planned the study, YDK: Collected and analyzed the data, YDK : Wrote the first draft of the manuscript. Both authors contributed to the interpretation of findings and reviewed the manuscript. They read and approved the final version of the article.

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Efficacy of high–versus moderate-dose statin therapy on lower extremity artery disease after revascularization

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ABSTRACT

Aim: Statins are one of the most important agents in the treatment of atherosclerotic peripheral arterial disease. We aim to compare high – and moderate-dose statin therapy in patients with lower extremity artery disease (LEAD) who have undergone percutaneous transluminal angioplasty (PTA).

Patients and Methods: Ninety-four patients treated with PTA were selected consecutively and retrospectively and were divided into two groups according to the high – or moderate-dose statin treatments they were given. Groups were compared for the absence of restenosis and occlusion as primary patency and the need for reintervention in the treated arterial segment as secondary patency. All patients underwent computed tomography (CT) angiography or duplex scan one year after receiving PTA.

Results: Coronary revascularization (p<0.001) and prior statin usage (p:0.02) were more common in the high-dose statin group when compared to the moderate-dose statin group. Lesion characteristics did not differ between the two groups. Primary patency rate was significantly higher (36.1% vs. 27.6%, p 0.01) in the high-dose statin group. Major amputation (4.2% vs. 10.6%, p:0.03) and minor amputation (12.7% vs. 19.1%, p:0.03) rates were significantly lower in the high-dose statin group. Regression analysis revealed that the usage of high-dose statin therapy was an independent predictor of higher primary patency in patients who were treated with prior PTA(Odds ratio:2.208, p<0.001)

Conclusion: High-dose long-term statin treatment might have better outcomes on primary patency in patients who underwent prior PTA for infrapopliteal lesions as a subgroup of peripheral artery disease. The administration of the high-dose long-term statin therapy might be important in the prognosis of peripheral arterial disease, especially for those with infrapopliteal lesions.

Keywords: Statin treatment, Percutaneous transluminal angioplasty, Peripheral artery disease

1. INTRODUCTION

Statins are competitive inhibitors of hydroxymethylglutaryl (HMG) CoA reductase, the rate-limiting step in cholesterol biosynthesis. They occupy a portion of the binding site of HMG CoA, blocking access of this substrate to the active site on the enzyme [1]. Statins are one of the main agents in cardiovascular disease in primary and secondary prevention [2]. In addition to coronary heart disease, peripheral artery disease and cerebrovascular events play a major role in secondary prevention. According to the 2019 European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias and the lipid modification to reduce cardiovascular risk, intensive statin therapy is recommended especially in patients with clinical atherosclerotic disease, under the age of 75 years old and with atherosclerotic cardiovascular disease (ASCVD) risk>7.5% [3].

In observational studies and limited randomized clinical trials (RCTs) in patients with lower extremity artery disease (LEAD) (from asymptomatic to severe cases), statin therapy has been shown to cause reductions in all-cause mortality and in cardiovascular (CV) events [4-6]. A systematic review

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of 18 trials including 10 000 patients with cholesterol levels ranging from normal to elevated has reported that lipid-lowering therapy in subjects affected by atherosclerosis of the lower limbs is associated with a 20% reduction in total CV events, together with a non-significant 14% reduction in all-cause mortality. Regarding limb prognosis, in the Reduction of Atherothrombosis for Continued Health (REACH) registry, statin use was associated with an 18% lower rate of adverse limb outcome [4,7].

Infrapopliteal occlusive disease (IP) is a severe and diffuse form of peripheral artery disease (PAD) and requires challenging revascularization procedures. Patients suffering from severe lifestyle-limiting claudication or critical limb ischemia due to atherosclerosis of the crural arteries are often frailer and have higher amputation and mortality rates [8]. In stenotic lesions and short occlusions, endovascular therapy can be the first choice. In long occlusions of crural arteries, bypass with an autologous vein gives superior long-term patency and leg survival. If the patient has increased risk regarding surgery or does not have an autologous vein, endovascular therapy may be attempted [9].

It is important that patients with infrapopliteal lesions receive the best medical treatment (such as lifestyle modification, cessation of smoking, pharmaceutical treatment) as in all atherosclerotic diseases after revascularization [2]. As already mentioned, high doses of statin should be used in patients with clinical atherosclerotic disease. In this study, we aimed to investigate whether there is any difference between vascular patency between two groups receiving high-dose statin and moderate-dose statin in a 1-year follow-up of infrapopliteal lesions after revascularization.

2. PATIENTS and METHODS

This study was performed retrospectively. All patients had been primarily treated with percutaneous transluminal angioplasty (PTA) of at least one infrapopliteal artery causing severe symptoms or critical limb ischemia (CLI) (Rutherford category 1–6). The indication of PTA was determined based on the 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases [10]. A total 126 limbs of 114 patients were consecutively evaluated. Significant stenosis of inflow arteries if present had to be treated successfully prior to enrollment. The success rate was 92.9% (106 patients) and technically successful angioplasty of de novo lesions were included. CLI is defined as the presence of chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven IP [11].

Technical success of infrapopliteal PTA was described as recanalization with antegrade flow and 30% or less residual stenosis below the knee artery. PTA was performed through anterograde (ipsilateral or contralateral) or retrograde approach at the discretion of the treating interventional cardiologist. Stents were implanted if flow-limiting complications occurred. Unless contraindicated, all patients received aspirin, clopidogrel, high-dose statin (80mg atorvastatin), and cilostazol for at least 1 month after successful recanalization of the vessel. According to the 2019 ESC/EAS guidelines for the management of dyslipidaemias, high-intensity statins received strong Class I recommendations for patients with clinical cardiovascular disease. High-intensity statins are defined as atorvastatin dose of 40–80 mg, and rosuvastatin dose of 20-40 mg. Moderate intensity statins are defined as atorvastatin dose of 10–20 mg, and rosuvastatin dose of 10 mg [3]. At follow-up, the patients' statin therapy was determined based on 2019 ESC/EAS guidelines for the management of dyslipidaemias guidelines after the PTA [3].

A total number of 126 limbs in 114 patients who underwent PTA were initially reviewed. Twenty patients (17.5%) were excluded from the study. 9 patients were excluded since they were not on statin therapy (n=9, 45%), 6 patients were excluded because they were not on high-dose statin therapy (n=6, 20%), and 5 patients were excluded for not following up (n=5, 25%). The remaining eligible patients were divided into two groups according to the statin dose as high – and moderate-dose. Patients were evaluated for primary patency, secondary patency, major and minor amputations and these were identified as clinical outcome. All patients underwent CT angiography or duplex scan a year after the PTA. Loss of patency is defined as restenosis (> 50%) or occlusion of the treated artery was detected by CT angiography or duplex scan. Primary patency was defined as the absence of restenosis, occlusion, or need for re-intervention in the treated arterial segment. Secondary patency was defined as utilizing secondary endoluminal procedures, which involved recanalizing occluded arterial segments. Major amputation was defined as limb loss above the metatarsal level, whereas minor amputation referred to trans metatarsal amputation or removal of more distal parts of the lower extremity.

The present study complies with the principles outlined in the Declaration of Helsinki. The study was approved by the Ethics Committee of Kartal Koşuyolu Heart and Vascular Diseases Research and Training Hospital (protocol number: 2019.7/18-234), and written informed consent was obtained from all participated patients.

Statistical Analysis

All statistical analyses were investigated using a software program (SPSS 22.0 for Mac; SPSS Inc., Chicago, IL, USA). The variables were determined using visual (histograms and probability plots) and analytic methods (Kolmogorov–Smirnov and Shapiro–Wilk tests) to assign whether or not they are normally distributed. Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean±standard deviation. Since all continuous variables were normally distributed, statistical comparisons of quantitative data were performed by an unpaired sample t-test. Logistic regression analyses were performed to determine the predictors of higher primary patency after one year PTA. A p-value of <0.05 was considered statistically significant.

3. RESULTS

After the exclusions, we identified 94 patients (77[78.7%] male, 61.7±8.4) who underwent PTA during the study period. Patients were divided into two groups according to the dose of

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statin treatment they received. The first group received a high-dose statin therapy (47 patients), and the second group received a moderate-dose statin therapy (47 patients).

Clinical characteristics of patients and lesion features of the two groups were summarized in Table I. Arrhythmia (p=0.03), coronary artery disease (p=0.01), coronary revascularization with CABG or PCI (p<0.001) and prior statin usage (p:0.02) were more common in the high-dose statin group. Lesion characteristics did not differ between the groups. There was a statistically significant difference in the clinical outcomes between the two groups. Primary patency rate was significantly higher (36.1% vs. 27.6%, p 0.01) in the high-dose statin group. Major amputation (4.2% vs. 10.6%, p:0.03) and minor amputation (12.7% vs. 19.1%, p:0.03) rates were significantly lower in the high-dose statin group. Clinical outcomes were summarized in Table II.

Univariate logistic regression analysis was performed to determine the independent predictors of higher primary patency after one-year PTA (Table III). The use of high-dose statin therapy was found to be an independent predictor of higher primary patency in patients who had received prior PTA (Odds Ratio: 2.208; 95% confidence interval:1.348-3.899; p<0.001).

Table I. *Clinical characteristics of patients and lesion features with respect to high dose statin usage*

Characteristics	High-dose statin group (n=47)	Moderate-dose statin group (n=47)	P value
Age, years	61.3±8.1	62.1±8.6	0.72
Male sex , n (%)	37 (78.7%)	40 (85.1%)	0.16
Diabetes, n (%)	42 (89.3%)	41 (8%)	0.53
Arrhythmia, n (%)	14 (29.7%)	8 (17.7%)	**0.03**
Congestive heart failure, n (%)	16(34%)	14(29.7%)	0.24
Coronary artery disease, n (%)	38(80.8%)	20 (42.5%)	**0.01**
CABG or PCI, n (%)	36 (76.9%)	13 (27.6%)	**<0.001**
Hypertension, n (%)	41 (87.2%)	43(91.1%)	0.34
Renal insufficiency, n (%)	27 (57.4%)	30 (63.8%)	0.54
Dialysis, n (%)	12 (25.5%)	14 (29.7%)	0.21
Stroke, n (%)	5(0.10%)	3(0.06%)	0.20
Current smoker, n (%)	42(89.3%)	40 (85.1%)	0.74
Chronic obstructive pulmonary disease, n (%)	21(44.6%)	17 (36.1%)	0.08
Serum total cholesterol (mg/dl)	216±35	234±56	0.08
Serum LDL (mg/dl)	128±23	134±36	0.09
Prior statin usage n (%)	25 (53.1%)	17 (36.1%)	**0.02**
Rutherford category, n (%) 4. 5. 6.	 17(36.1%) 20(42.5%) 10((21.2%)	 20(42.5%) 19(40.4%) 8(17%)	 0.09
Previous higher level revascularisation, n (%)	13(27.6%)	16 (34%)	0.11
Target artery, n (total) Anterior tibial Peroneal Posterior tibial Tibioperoneal trunk	 21 (75) 12 (75) 39 (75) 3 (75)	 28 (66) 11 (66) 22 (66) 5 (66)	 0.28
Lesion length, cm	12±3	11.3±3	0.41
Baseline stenosis, %	79±13	75±12	0.21
Total Occlusions, n (%)	38 (80.8%)	35 (74.4%)	0.41
Severe Calcification, n (%)	31 (65.9%)	28 (59.5%)	0.35
Below the ankle lesion, n (%)	11(23.4%)	8 (17%)	0.09
TAsc 2 classification A,B,C D	 16 (34%) 31 (66%)	 17 (36%) 30 (64%)	 0.5 0.5

CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, TASC: trans atlantic inter-society consensus

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Table II. *Clinical endpoints after one-year PTA*

	High-dose statin group (n=47)	Moderate-dose statin group (n=47)	P value
Primary patency	17 (36.1%)	13 (27.6%)	**0.01**
Secondary patency	15 (31.9%)	18(38.2%)	0.07
Major amputation	2 (4.2%)	5 (10.6%)	**0.03**
Minor amputation	6 (12.7%)	9 (19.1%)	**0.03**

Bold values indicate statistical significance p<0.05

Table III. *Univariate logistic regression analysis to determinate the predictors of higher primary patency after one-year PTA*

	Odds Ratio	95% Confidence Interval	p
Usage of high-dose statin therapy	2.208	1.348-3.899	**<0.001**
Age	1.010	1.002 – 1.017	0.029
Male sex	1.061	0.42-2.62	0.59
Severe calcification at lesion	1.024	1.001-1.169	0.36
Lesion length	1.008	0.97-1.204	0.48

Bold values indicate statistical significance p<0.05

4. DISCUSSION

The present study evaluated the long term effects of high-dose statin treatment compared to moderate-dose statin therapy in patients with infrapopliteal artery disease who had undergone successful PTA. The findings of our study show that the primary patency rate was significantly higher in the high-dose statin therapy group, while major amputation and minor amputation rates were significantly lower in the high-dose statin group. The use of high-dose statin therapy was an independent predictor of higher primary patency in patients who had received prior PTA.

Although, it is known that high cholesterol concentrations are associated with a higher risk of developing PAD [12], statins are underprescribed in PAD when compared to other well-known atherosclerotic disease processes [13]. The intensity of statin therapy has also been a matter of debate and the effect of high-intensity statin therapy on cardiovascular outcomes is not well understood in patients with PAD [14,15]. Clinical studies on femoral plaque characteristics have reported the use of high-dose statins to predominantly improve plaque composition or cause plaque regression, leading to a more stable phenotype in PAD [6]. Arya et al. showed that amputation mortality rates were lower in the group receiving high-dose statins in patients with PAD. This study showed an almost 30% reduction in risk of death and 30-40% reduction in risk of major amputation in high-intensity statin group. In low and moderate-intensity statin group, extremity loss and mortality were also reduced but not as high as in the high-intensity group [16]. Foley et al. revealed that patients with PAD who were on high-dose statin therapy before receiving endovascular intervention showed improved survival and fewer major adverse cardiovascular events compared to patients on moderate-dose statin therapy. However, they did not find any significant difference in the follow-up patency of lower extremity arteries between the 2 groups [17]. Stoekenborek et al. showed that high-dose statin therapy with atorvastatin significantly reduced the incidence of PAD compared with moderate-dose statin therapy with simvastatin [18]. Spring et al. investigated the effect of high-dose atorvastatin on endothelial function and local progression of the disease in patients with PAD. However, they did not find any significant difference between the use of high – and moderate-dose statin therapies [19]. As shown in the literature, the use of statin therapy shows improvement in both plaque stabilization and reduces inflamation in patients with a wide range of atherosclerotic diseases. In our study, we found similar results, that a high dose statin therapy was an effective treatment for atherosclerotic lesions. The high-dose statin group showed statistically significant better outcomes in all the variables we tested. Even though in the literature there are limited studies showing no statistically significant improvements with the use of statin therapy, most of the studies come to a similar conclusion that a high-dose statin therapy provides better overall outcome in atherosclerotic diseases [6,16,18,19].

Infrapopliteal occlusive disease (IP) is a severe and diffuse form of PAD and requires challenging revascularization procedures. Patients suffering from severe lifestyle-limiting claudication or CLI due to atherosclerosis of the crural arteries are often frailer and have higher amputation and mortality rates [8]. Revascularization of infrapopliteal lesions are predominantly treated with endovascular intervention although revascularization options vary depending on the length of the lesion, the presence or absence of an autologous venous graft, and the surgical risk [9]. PTA remained the most widely used method for recanalization of the infrapopliteal lesions but was significantly limited by the high restenosis and occlusion rates [20]. A meta-analysis by Romiti et al of infrapopliteal angioplasty for the treatment of CLI showed 1-year primary and secondary patency rates of 58% and 68%, respectively [21]. Another study showed primary patency at 1 year of 33% with secondary patency of 56% and a limb salvage rate of 75% after infrapopliteal angioplasty [22].

High-dose statin therapy is of great importance in the prevention of atherosclerotic cardiovascular diseases and in the prevention of disease progression with both reduction of cholesterol levels and pleitrophic effects in patients with PAD.

Statins have great importance in the prevention of atherosclerotic disease progression by lowering cholesterol levels [2]. In addition to achieving a therapeutic decrease in serum cholesterol levels, statin therapy appears to promote other effects that are independent of changes in serum cholesterol. The effect of statins on the endothelial function in humans remains under discussion. Particularly, it is still unclear if the improvement in endothelial function is due to a reduction in LDL-cholesterol or an arterial pleiotropic effect. These pleiotropic effects include attenuation of vascular inflammation, improved endothelial cell function, stabilization of atherosclerotic plaque, decreased

vascular smooth muscle cell migration and proliferation, and inhibition of platelet aggregation [23]. Silva et al. showed that the pleiotropic effects of high-dose statins may improve outcomes in atherosclerotic renovascular disease [24]. Subramanian et al. showed that high-dose atorvastatin reduces periodontal inflammation, suggesting a newly recognized effect of statins. Given the concomitant changes observed in periodontal and arterial inflammation, these data raise the possibility that a portion of that beneficial impact of statins on atherosclerosis relates to reductions in extra-arterial inflammation [25].

Study limitations

Our study has several limitations. First, our study was a single-center and non-randomized study. Secondly, a relatively small number of the patients were enrolled in our study. Thirdly, the procedures were not performed by a single team, and even though all the operators were experienced interventional cardiologists, revascularization strategy was at the discretion of the operator. Also, the high-dose statin treatment group had lower low-density lipoprotein (LDL) cholesterol levels compared to the moderate-statin treatment group although it was statistically insignificant. However, based on the 2019 ESC/EAS guidelines for the management of dyslipidaemias guideline, the LDL cholesterol level should be <70 mg/dL [3]. This value might affect the findings of our study.

Conclusion

Statins are of great importance in improving cardiovascular protection, inhibiting the progression of PAD, and improving clinical outcomes after interventional therapy in PAD. High-dose long-term statin treatment might have better outcomes on primary patency in infrapopliteal lesions as a subgroup of PAD after PTA. The administration of the high-dose long-term statin therapy might be important in the prognosis of patients with infrapopliteal lesions. Further multi-centered and randomized clinical studies are needed to clarify the possible causal relationship.

Compliance with the Ethical Standards

Ethical Approval:

The present study complies with the principles outlined in the Declaration of Helsinki. The study was approved by the Ethics Committee of Kartal Koşuyolu Heart and Vascular Diseases Research and Training Hospital, Istanbul (protocol number: 2019.7/18-234), and written informed consent was obtained from all participated patients

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Author contributions:

All authors contributed to the study conception and design. AK was the primary investigator of the study, AK:Design of the study, data collection, analysis of the data and drafting of the article, BK and AK: Critical revision of the article, AU, RZ, and DA: Analysis and collecting of the data and drafting of the article. All authors read and approved the final version of the article.

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Morphometric analysis of middle and posterior cranial fossae foramina in 3D reconstructions of CT images: A midline asymmetry evaluation

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ABSTRACT

Objective: The cranial base harbours numerous foramina, and the anatomical properties of the foramina are crucial in clinical interventions. The purpose of the current study is to evaluate possible asymmetries regarding the middle and posterior cranial fossae foramina using 3D reconstructions of high-resolution computed tomography (CT) images.

Patients and Methods: High-resolution cranial CT images of 253 female and 287 male adult patients were used in the study. The patients were 18 to 40 years of age without any apparent cranial pathology. The distances from the foramen rotundum, foramen ovale, foramen spinosum, internal acoustic meatus, hypoglossal canal to the midline were measured bilaterally to compare both sides.

Results: The foramen spinosum and the mid-clival line measurements demonstrated statistically significant results favoring the right side (p=0.03, right mean 3.052 ± 0.253 cm, left mean 2.982 ± 0.193 cm). In males, the right foramen spinosum to mid-clival line measurements were significantly longer than the left side (p=0.027, right mean 3.150 ± 0.250 cm, left mean 3.070 ± 0.180 cm).

Conclusion: As predicted, the male measurements were significantly longer than the female measurements regardless of sides in all measurements. The measurements of cranial asymmetries may help describe anomalies and may contribute to the clinical approaches.

Keywords: Asymmetry, Computed tomography, Cranial fossa, Foramen, Midline

1.INTRODUCTION

Asymmetry has long been a topic of interest among many disciplines and there are different views in the literature regarding the concept of symmetry in the human body. Some researchers state that asymmetry is diverse, but according to some, there is apparent lateralization [1].

Although, the human skull is generally assumed as symmetric, asymmetry of the human skull base is an expected and a very common finding observed in morphometric measurement studies [2]. Environmental and genetic factors, and certain pathologies may affect the developmental entities and cause dissimilarities in the right and left measurements [3]. According to the studies performed on cephalometric X-ray graphies, the right side of the skull is observed larger than the left side. This difference is assumed to be due to the developmental properties of the human brain [2]. Accordingly, it is very crucial and yet very hard to understand whether the asymmetry is abnormal or is within normal limits [3].

Certain asymmetries may affect the anatomical structure of the skull base accommodating the foramina through which prominent neurovascular structures enter or exit the skull [4,5]. Since, the middle cranial fossa articulates with the bony framework of the face, these corresponding structures may influence each other reciprocally in means of developmental morphology [6].

The structural relationship among the skull base foramina is crucial in identifying certain pathologies, evaluating neurological disorders, and performing skull base surgical interventions [4,5,7,8,9]. For instance, detailed information concerning the foramen ovale (FO) and the foramen spinosum (FS) is significant in identifying nasopharyngeal and middle cranial fossa lesions such as abnormal enlargements in the foramen ovale may suggest trigeminal neurinomas [10,11].

The foramen spinosum has also been a widely studied structure since it permits the passage of the middle meningeal artery,

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which is used as a bypass graft material in the internal carotid artery and the posterior cerebral artery interventions [12,13].

The posterior cranial fossa harbours the petroclival region and important foramina, therefore it has been of utmost importance for certain neurological interventions [14]. The trans-sphenoidal, anterior, lateral, presigmodial, retrosigmoidal and the transcondylar approaches require detailed structural knowledge concerning the region [15,16].

Finally, the gender difference among the measurements is also valuable for forensic sciences, anthropology, and archaeology [7]. This study aims to identify possible asymmetries and gender differences in the middle and posterior cranial fossae foramina and provide normative data in the population using high-resolution computed tomography (CT) images obtained from the Turkish population in our institution.

2. MATERIALS and METHODS

The study was approved by the Ethics Committee for Clinical Research of Marmara University, Shool of Medicine with the protocol number 09.2019.477. Patient information remained confidential and solely used for scientific purposes.

The images used in the study were obtained from the School of Medicine Department of Radiology. High-resolution cranial CT images of 253 female and 287 male Caucasian adult patients who were referred to the Department of Radiology from October 2019 to February 2020 were taken into consideration.

The images were chosen from the thin section cases referred from various clinics to rule out cranial pathologies. The patients were 18 to 40 years of age without any apparent cranial pathology. The mean age was 28.25 ± 0.8256 for the male patients and 30.36 ± 0.8088 for the females.

Imaging was performed on a 256 channel (2x128) Multidetector Computed Tomography Scanner (Somatom Definiton Flash, Siemens Healthcare; Erlangen, Germany). Images were obtained in the axial plane with 0.6 mm collimation and 120 kVp (kilovolt peak). mAs (milliamperes per second) were adjusted for each patient via tube current modulation.

After the scan, high-resolution images (0.6 mm slice thickness) were reconstructed in sagittal and coronal planes. The images were evaluated utilizing RadiAnt Dicom Viewer 4.2.1 free version. The images were transferred to the software and 3D multiplanar reconstruction (MPR) was applied to the images. In 3D MPR reconstructions, tilt corrections were made to achieve a true positioning in sagittal, coronal, and axial axes.

The calvariae of the images, cervical vertebrae in the scanning area, together with excessive lateral areas of the skull were removed to enhance the measuring process in 3D measurements. MPR measurements were used to confirm the consistency of the 3D data. The mid-clival line passing through the basion and the mid-point of the dorsum sella was marked as the midline [14,17,18]. The distances between the medial rims of the foramen rotundum (FR), FO, FS, internal acoustic meatus (IAM), hypoglossal canal (HC), and the mid-clival midline reference were measured bilaterally to compare both sides (Figure 1). All measurements were performed randomly by the same expert investigator for the right and left sides.

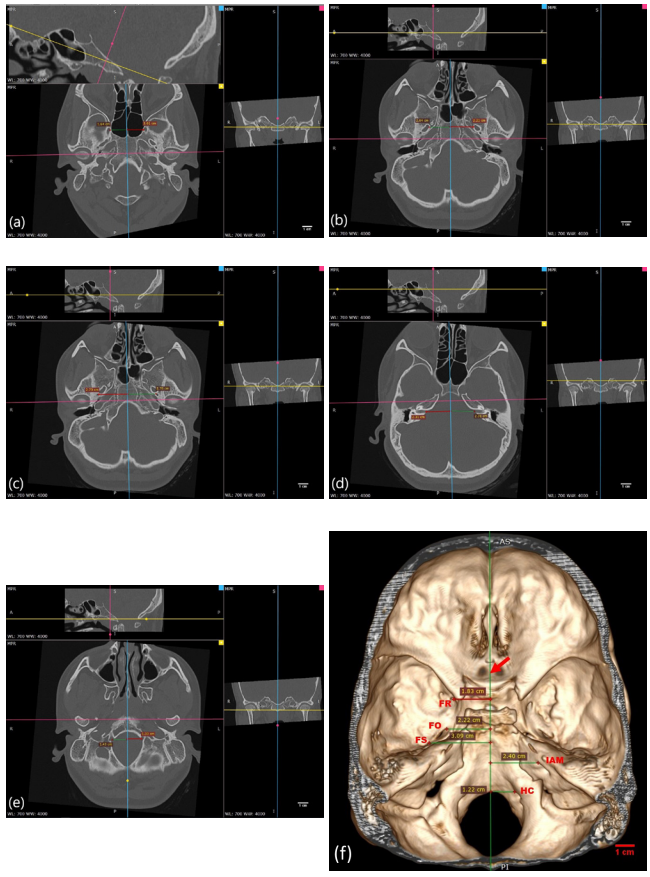

Figure 1 a. *Bilateral foramen rotundum to the midline measurement sample in axial sections of multiplanar reconstruction. Coronal and sagittal sections were included to demonstrate the tilt correction. The blue line represents the midline.*
b. Bilateral foramen ovale to the midline measurement sample in axial sections of multiplanar reconstruction. Coronal and sagittal sections were included to demonstrate the tilt correction. The blue line represents the midline.
c. Bilateral foramen spinosum to the midline measurement sample in axial sections of multiplanar reconstruction. Coronal and sagittal sections were included to demonstrate the tilt correction. The blue line represents the midline.
d. Bilateral internal acoustic meatus to the midline measurement sample in axial sections of multiplanar reconstruction. Coronal and sagittal sections were included to demonstrate the tilt correction. The blue line represents the midline.
e. Bilateral hypoglossal canal to the midline measurement sample in axial sections of multiplanar reconstruction. Coronal and sagittal sections were included to demonstrate the tilt correction. The blue line represents the midline.
f. A measurement sample of the cranial fossae foramina to the midline in the 3D reconstruction of high-resolution CT images. The red arrow represents the midline,

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Statistical Analysis

Statistical Package for the Social Sciences version 15.0 was used for the statistical analysis of the data. Assumption of normality was tested using the Kolmogorov-Smirnov test and the mean comparisons of the independent groups were tested via unpaired t-test. The Pearson correlation coefficient was calculated and the correlation among the data was tested. P<0.05 was accepted to be significant.

3. RESULTS

The comparison of gender measurements regardless of sides was found to be longer in the males than the females as expected. Regardless of the gender difference, side comparisons of the FR, FO, HC, and the IAM to the midline reference measurements were statistically insignificant. However, when the FS and the midline reference measurements were taken into account, the comparison demonstrated statistically significant results favoring the right side shown in Table I (p=0.03, right mean 3.052 ± 0.253 cm, left mean 2.982 ± 0.193 cm).

In females, all measurements of the related structures were compared in means of side differences, and no statistical significance was found. When the right side measurements were compared among the genders, FS, IAM, FR and FO measurements were statistically significant, favoring the male measurements (p<0.0001 for FS and IAM; p=0.027 for FR; p=0.017 for FO), but HC measurements were not significant. For the left side comparison among the genders FO, FS, HC and IAM measurements were longer in males (p<0.0001 for FO, FS and IAM; p=0.015 for HC), but FR measurements failed to demonstrate statistical significance (Table I). The right FS to midline measurements in males were significantly longer than the left side (p=0.027) (Table I). When the general correlation is considered, all variables demonstrated a linear but poor relationship.

Table I. *Mean distances measured from the medial rims of the foramina to the midline*

	Foramen Rotundum		Foramen Ovale		Foramen Spinosum		Hypoglossal Canal		Internal Acoustic Meatus	
	Mean ± SD (cm)	Significance	Mean ± SD (cm)	Significance	Mean ± SD (cm)	Significance	Mean ± SD (cm)	Significance	Mean ± SD (cm)	Significance
Female (n= 110)	1.640 ± 0.271	0.005**	2.211 ± 0.163	<0.0001**	2.911 ± 0.172	<0.0001**	1.401 ± 0.160	0.004**	2.380 ± 0.290	<0.0001**
Male (n= 128)	1.741 ± 0.292		2.310 ± 0.192		3.110 ± 0.221		1.460 ± 0.162		2.661 ± 0.292	
Right (n= 119)	1.682 ± 0.271	0.418	2.281 ± 0.182	0.241	3.052 ± 0.253	0.03*	1.453 ± 0.172	0.069	2.563 ± 0.341	0.237
Left (n= 119)	1.711 ± 0.293		2.253 ± 0.191		2.982 ± 0.193		1.412 ± 0.151		2.512 ± 0.311	
Female – Right (n= 55)	1.621 ± 0.261	0.027*	2.241 ± 0.171	0.017*	2.931 ± 0.190	<0.0001**	1.423 ± 0.178	0.085	2.390 ± 0.272	<0.0001**
Male – Right (n= 64)	1.730 ± 0.272		2.320 ± 0.182		3.150 ± 0.250		1.474 ± 0.172		2.701 ± 0.330	
Female – Left (n= 55)	1.662 ± 0.273	0.081	2.180 ± 0.151	<0.0001**	2.890 ± 0.151	<0.0001**	1.371 ± 0.140	0.015*	2.371 ± 0.322	<0.0001**
Male – Left (n= 64)	1.751 ± 0.312		2.310 ± 0.202		3.070 ± 0.180		1.440 ± 0.152		2.622 ± 0.256	
Female – Right (n= 55)	1.621 ± 0.261	0.442	2.241 ± 0.171	0.094	2.931 ± 0.190	0.295	1.423 ± 0.178	0.143	2.390 ± 0.272	0.743
Female – Left (n= 55)	1.662 ± 0.273		2.180 ± 0.151		2.890 ± 0.151		1.371 ± 0.140		2.371 ± 0.322	
Male – Right (n= 64)	1.730 ± 0.272	0.674	2.320 ± 0.182	0.815	3.150 ± 0.250	0.027*	1.474 ± 0.172	0.249	2.701 ± 0.330	0.142
Male – Left (n= 64)	1.751 ± 0.312		2.310 ± 0.202		3.070 ± 0.180		1.440 ± 0.152		2.622 ± 0.256	

** Significance at p <0.05*
*** Significance at p ≤ 0.005*

Table II. *Comparison of the mean measurements in the literature to the current study*

Authors	Lang et al. [23]	Sharma and Garud [18]	Sharma and Garud [19]	Unver Doğan et al. [26]	Somesh et al. (2015)	Chen et al. [31]	Mohebbi et al. [29]	Current Study
Research material	Dry skulls	Dry skulls	Dry skulls	Dry skulls	Dry skulls	CT Angiography Images	CT Images (3 mm slice thickness)	CT Images (0.6 mm slice thickness)
Reference point for Foramina	Center of foramen	Medial rim	Medial rim	Medial rim	Center of foramen	Medial rim	Medial rim	Medial rim
Right FR to ML Distance				1.799 ± 0.259 cm		1.751 ± 0.151 cm	1.900 ± 0.207 cm	1.682 ± 0.271 cm
Left FR to ML Distance				1.853 ± 0.241 cm		1.732 ± 0.144 cm	1.934 ± 0.217 cm	1.711 ± 0.293 cm
Right FO to ML Distance		2.213 cm		2.258 ± 0.299 cm				2.281 ± 0.182 cm
Left FO to ML Distance		2.171 cm		2.215 ± 0.241 cm				2.253 ± 0.191 cm
Right FS to ML Distance	2.808 cm	2.853 cm		2.861 ± 0.296 cm	3.039± 0.179 cm			3.052 ± 0.253 cm
Left FS to ML Distance	2.976 cm	2.813 cm		2.847 ± 0.297 cm	3.086 ± 0.15 cm			2.982 ± 0.193 cm
Right IAM to ML Distance								2.563 ± 0.341 cm
Left IAM to ML Distance								2.512 ± 0.311 cm
Right HC to ML Distance			1.680 cm					1.453 ± 0.172 cm
Left HC to ML Distance			1.668 cm					1.412 ± 0.151 cm

FO: *Foramen ovale,* ***FR:*** *Foramen rotundum,* ***FS:*** *Foramen spinosum,* ***HC:*** *Hypoglossal canal,* ***IAM:*** *Internal acoustic meatus,* ***ML:*** *midline*

4. DISCUSSION

Briefly, the current results demonstrate that the FS to midline measurements reveal statistical significance favoring the right side in gender-neutral comparison and in the male population but not in the female group in regards to asymmetry. In contrast to the general assumption, the left side comparison of the FR and the right side comparison of the HC among the gender groups were statistically insignificant. Some of the current results were in concordance with the literature but some were not, where the literature in itself, is mainly insufficient in providing consistent data concerning the skull base asymmetries [21].

Asymmetry is generally observed in the skull base due to its close relationship with the developing neurological structures [2]. Cranial asymmetries without any pathological conditions and functional anomalies should be taken into consideration since they may be of importance to prevent certain malpractice cases [20].

Generally, the studies concerning the cranial fossa foramina to the midline measurements were performed on dry skulls [23-28] and they provided limited results for they were restricted to a single structure, lacking to provide a collective measurement perspective to several foramina. Additionally, only one study used adult CT images for the measurements, again dealing with a restricted set of structures measured, utilizing 3 mm slice thickness. In the current study, the image resolution was higher, therefore, image reconstruction quality was more precise with the slice thickness of 0.6 mm. In terms of the measurement landmarks, five of these studies measured the midline distance from the medial rims of the foramina, two of them from the centers of the foramina and one did not specify the measurement landmark of the foramina. In the current study, medial rims of the foramina were used as the foraminal landmark.

The mid-region of the cranial base is structurally more stable than the lateral regions [20]. Especially the regions containing FS, stylomastoid foramen, and the foramen magnum are not generally susceptible to symmetry changes [22], but in the current study, the results demonstrated significantly longer measurements on the right FS in gender-neutral comparison and in male population right and left side comparison (Table 1). This finding may contribute to the interventions in the mid-region of the cranial base, especially in FS where asymmetry is not prominently expected.

In another study, conducted in dry human skulls, the distances of the FO and the FS to the midline were found shorter to the left side when compared to the right [23]. In the current study, both right and left FO measurements to the midline were very similar with longer measurements on the right side without a statistical significance. Regarding the FS measurements in the current study, the right side measurements were longer in males with a statistical significance, whereas in females, there were no significant results. Table II demonstrates a comprehensive comparison of the literature together with the current study.

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The studies concerning the skulls may provide accurate measurements in means of demonstrating physical distance. However, the devices used in the measurements may not reach or fit the reference points or they may damage the bony structure. Our measurements which are conducted in 3D high-resolution CT reconstruction images do not represent the physical distance but they are superior in demonstrating asymmetries due to the ease of referencing measurement landmarks. Furthermore, the current measurements may be superior to dry skull measurements because high-resolution radiological images represent the living tissue since dry skull structures may be damaged due to the natural progressions and clinical cases require radiological imaging of the skull base region for preoperative evaluation.

Measurement data and asymmetry information may also be very important in identifying occult pathologies since larger than expected asymmetries may be the only finding encountered in these cases such as cystic adenoid carcinoma, which may cause osteolytic lesions may affect the foramina of the skull base [30,31].

Conclusion

The skull base is very complicated in means of its structural and numerous foramina content. The variations concerning the region are substantial in the interventions of the area [19]. Presumably, the measurements of cranial asymmetries may help describe anomalies encountered in radiological evaluations and may contribute to the surgical interventions related to the region. The current study is the first to comprehensively demonstrate the middle and posterior cranial fossae foramina to the midline measurements in 3D reconstructions of high-resolution CT images.

Compliance with the Ethical Standards

Ethical Approval: The study was approved by the Clinical Research Ethics Committee of Marmara University, School of Medicine, Istanbul with the protocol number 09.2019.477. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Financial Support: The authors have no relevant financial information to close.

Conflict of Interest: The authors have no potential conflicts of interest to disclose

Author Contributions: UV: Study conception, design, data analysis, interpretation of results, draft manuscript preparation, OB: Design, data analysis, SDY: Data gathering and analysis, EO: Data gathering and analysis, NB: Data analysis, statistical analysis, and design, OO: Study conception, design, interpretation of results. All authors reviewed the results and approved the final version of the manuscript.

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Reliability of coeliac and superior mesenteric artery origin level in lumbosacral transitional vertebrae detection and vertebral numbering

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ABSTRACT

Objective: To evaluate the value of coeliac artery (CA) and superior mesenteric artery (SMA) origin levels as an anatomic marker in the detection of lumbosacral transitional vertebrae (LSTV) and vertebral enumeration.

Patients and Methods: Institutional review board approval was obtained. Routine lumbar magnetic resonance (MR) imaging that included sagittal cervicothoracic scout images in 972 cases were evaluated retrospectively. Six segments were created in the vertebral column with 7 lines. CA and SMA ostiums were localized in these segments.

Results: Coeliac artery and SMA levels were detected more caudally in lumbarized S1 and more cranially in sacralized L5 cases compared to non-LSTV cases.

Conclusion: Coeliac artery and SMA origin levels as anatomical markers are not dependable for vertebral numbering due to their wide variability.

Keywords: Lumbosacral transitional vertebrae, Coeliac artery, Superior mesenteric artery, Vertebral enumeration, Magnetic resonance imaging

1. INTRODUCTION

The lumbosacral transitional vertebrae (LSTV) are defined as congenital spinal anomalies consisting of sacralization of the lower lumbar vertebral segment or lumbarization of the upper sacral vertebral segment. The prevalence of LSTV in the general population was reported as between 4% and 30% [1,2].

Computerized tomography (CT) is considered to be the best imaging method for detecting LSTV due to high spatial resolution. However, CT imaging with the indication for LSTV would unnecessarily cause ionizing radiation exposure. In addition, CT is not a preferred method in assessing non-traumatic back pain. In these clinical circumstances, magnetic resonance imaging (MRI) is often preferred, given its high contrast resolution in the vertebral column and surrounding soft tissues [1].

Magnetic resonance imaging has also some downsides in vertebral enumeration and detection of LSTV, such as limitation in visualizing the thoracolumbar component, inefficacy in the identification of transitional vertebra and failure to distinguish the hypoplastic rib and the prolonged transverse process of lumbar vertebrae.

The lumbosacral transitional vertebrae identification is crucial as incorrect vertebral numbering can cause clinically irrelevant radiologic findings and surgery at the wrong level [3]. In addition, the "Bertolotti syndrome" described by Mario Bertolotti in 1917, which relates LSTV to back pain, is a controversial subject [4].

A standard method for vertebral numbering has not been established. Sagittal cervicothoracic scout images can be used if images are available. Otherwise; aortic bifurcation, right renal artery origin, conus medullaris or iliolumbar ligament level determination can be used as an anatomical indicator. However, all these techniques can lead to inaccurate results [5,6].

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In this study, we aimed to clarify the effectiveness of the coeliac artery (CA) and superior mesenteric artery (SMA) in vertebral numbering and LSTV detection.

2. PATIENTS and METHODS

This study was approved by the Marmara University, School of Medicine Ethics Committee (approval number: 09.2015.354) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Magnetic resonans imaging findings of 972 patients with lower back pain or lumbar radiculopathy were evaluated retrospectively. Patients with a history of serious spinal or pelvic trauma, stage 2 and over spondylolisthesis, previous infection and lumbar spinal surgery were not included in the study because they may have changed the normal anatomy significantly. Cases with significant spinal malformation and severely torturous abdominal aortic aneurysms were not evaluated.

All images were acquired with a 3.0 Tesla MR device (Verio, Siemens Healthcare, Erlangen, Germany) using dedicated lumbar spinal coil with standard lumbar MR protocol and without contrast material. All studies included T2-weighted turbo spin echo (TSE) whole spinal column counter images. For the lumbosacral vertebral imaging; sagittal and axial T1-weighted TSE (TR/TE: 380/ 9.4ms) and T2-weighted TSE (TR/TE: 3390/106) were obtained. Axial images had a matrix of 256x133 with a slice thickness of 4mm and a gap of 0.4 mm and sagittal images had a matrix of 256x320 with a slice thickness of 4mm and a gap of 0.4 mm.

Two radiologists, with a spinal radiology experience of 10 years and 1 year, evaluated the images by consensus. Sagittal cervicothoracic counting images were used as the gold standard method for vertebral numbering. The cervicothoracic counting images of all cases were evaluated in terms of proficiency. Following this assessment, the vertebrae were numbered using the picture archiving and communications system (PACS) program with cross-link and vertebral labelling capabilities [ ] Cervical, thoracical, and lumbar vertebrae were numbered through the caudal direction from C2 (2nd cervical vertebra) level to S1 (1st sacral vertebra) level in cervicothoracic counting images; with the assumption that the cervical region carrying 7 vertebrae and the thoracic region carrying 12 vertebrae was the anatomical standard.

Sagittal T1 and T2, and axial T2 weighted images were used to assess the origin of CA and SMA. The first main vascular structure originating from the abdominal aorta was defined as the celiac truncus, and the second main vascular structure was defined as the SMA. These vascular structures were classified according to the vertebra corpus and intervertebral discs, where they were adjacent to the cross-link function. For standard assessment, the exit points from the aorta of the vascular structures were determined.

For scoring and statistical evaluation; six regions were created in the vertebral column with 7 lines passing through the middle of the T12-L1-L2 vertebra corpus and the T11-12, T12-L1, L1-L2 and L2-L3 intervertebral disc spaces. Starting from the cranial region, each region was numbered from 1 to 6, and the CA and SMA ostiums were located accordingly.

Anatomical structures located at the boundary of two regions were given the number of the region corresponding to the majority of the diameter percentages.The minimum and maximum values, mean, median and 95% confidence intervals for each parameter were calculated using this numbering system.

With this numbering; the area between the lines passing through the T11-T12 intervertebral disc space and the middle of the T12 vertebral corpus was identified as 1, between the middle of the T12 vertebral corpus and the T12-L1 intervertebral disc space as 2, between the T12-L1 intervertebral disc space and the middle of the L1 vertebral corpus as 3, between the middle of the L1 vertebra corpus and the L1-L2 intervertebral disc distance as 4, between the L1-L2 intervertebral disc distance and the middle of the L2 vertebra corpus as 5 and between the middle of L2 vertebra corpus and the L2-L3 intervertebral disc distance as 6 (Figure 1).

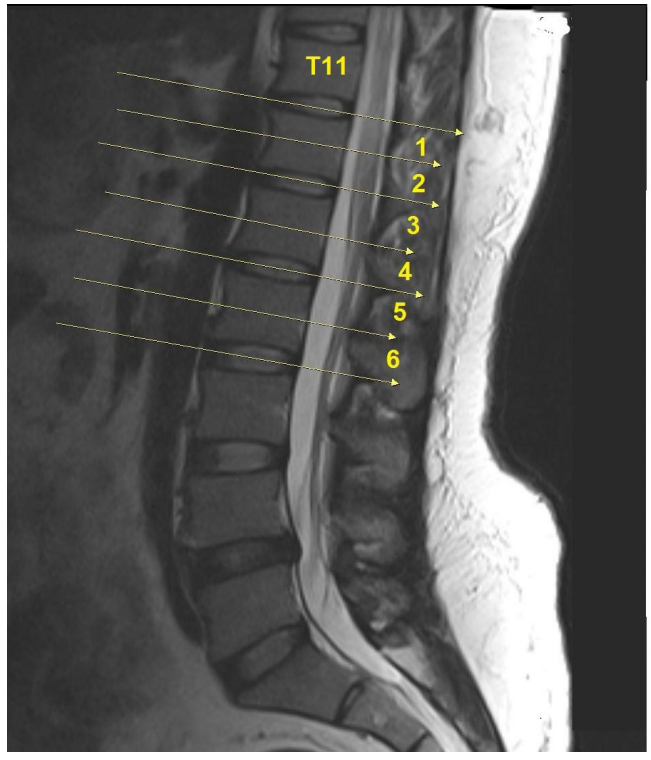

Figure 1. *Sagittal T2-weighted MRI. Six artificial segments with seven lines*

Finally, to evaluate the relationship between LSTV and disc degeneration, reduction of the intervertebral distance in the lumbar level was scored by numbering between 0 (none) and 5 (all levels).

Statistical Analysis

For the statistical analysis of the data obtained in the study, 'Statistical Package for Social Sciences' (SPSS, Chicago, USA) version 21.0 was used. Kolmogorov-Smirnov distribution test was used to determine descriptive statistical methods (frequency, mean, percentage, standard deviation) as well as normal distribution when study data were evaluated.

In the case of two or more groups in comparison of quantitative data; Kruskal Wallis test was used for comparison of non-normal

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distribution parameters between groups. Spearman correlation analysis was performed for the relationship of the parameters. P values less than 0.05 were considered statistically significant.

3. RESULTS

There were 597 female (61.4%) and 375 male (38.6%) patients in the study (F/M= 1.6). The mean age was 43.8.

The lumbosacral transitional vertebrae was detected in 178 (18.3%) of the 972 cases evaluated in the study. 125 of LSTV cases had sacralized L5 and the other 53 had lumbarized S1.

In all cases; the CA ostium level was located between the 1st and 4th regions. It was most frequently located in the second region (50.6% of cases), followed by Region 1 (30.2%) (Figure 2). In the non-LSTV group, the CA ostium level was mostly in the 2nd (56 %) and 1st regions a (27 %). In lumbarized S1 cases, it was in the 3rd (45 %) and 2nd regions (35 %) and in the 1st (72 %) and 2nd region (28 %) in sacralized L5 cases.

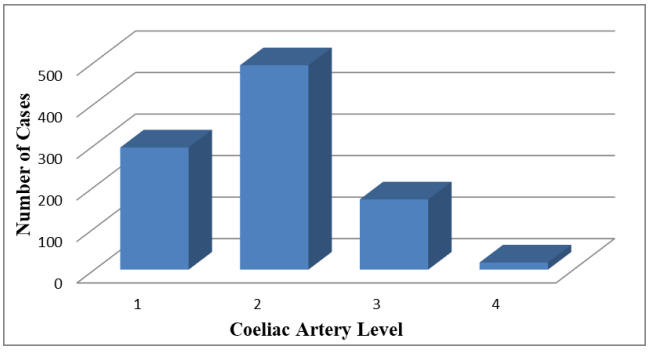

Figure 2. *Distribution of CA levels*

Overall SMA ostium level was observed between the 1st and 5th regions. SMA ostium level was most frequently located in the 3rd region (52.5 %), followed by the 2nd region (27.5 %) (Figure 3). In the non-LSTV group, it was mostly in the 3rd (59 %) and 2nd regions (25 %), whereas in sacralized L5 cases it was in the 2nd (64 %) and 3rd regions (28 %) , and in lumbarized S1 cases it was in the 4th (49 %) and 3rd regions (35 %).

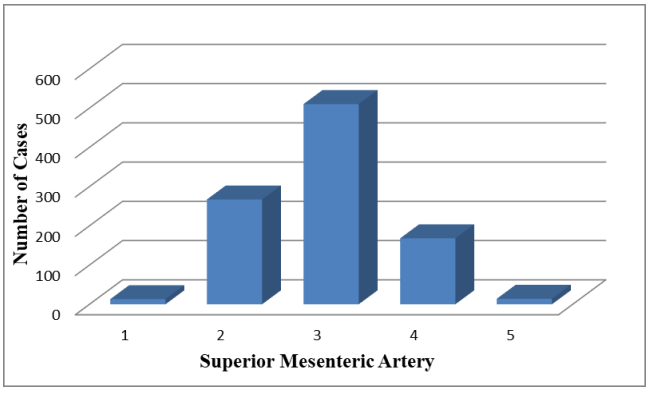

Figure 3. *Distribution of SMA levels*

According to these findings, CA and SMA levels showed a significant difference in distribution ($p<0.001$). In other words, CA and SMA are located higher in lumbarized S1 patients compared to non-LSTV cases. Similarly, CA and SMA of sacralized L5 cases are located lower than non-LSTV cases.

Accordingly, CA and SMA level were more caudally in lumbarized S1 and more cranially in sacralized L5 cases compared to non-LSTV cases.

Loss of disc height was not observed in 54.4% of cases, yet it was detected in 23.6% of the cases at one level, in 12.4% at two, in 5% at three, in 3% at four levels and in 1.5% at all levels. There was no significant difference in loss of disc height between the three groups (Non-LSTV, sacralized L5 and lumbarized S1) ($p = 0.335$).

4. DISCUSSION

The results of this study showed that CA and SMA origin levels are located more caudally in the case of the lumbarization and more cranially in the sacralization, and are not dependable for vertebral numbering.

The prevalence of LSTV in the literature is reported between 4% and 37%.

The systematic evaluation of some studies conducted between 2000 and 2020 found a mean LSTV prevalence of 19.4% [6-18]. LSTV was detected in 18.3% of 972 cases in our study. L5 sacralization was observed in 12.9% of all cases and S1 lumbarization was observed in 5.5% of all cases. These results are in the range of current literature in terms of LSTV prevalence.

In the current literature, some studies postulate a difference in LSTV prevalence in female and male patients. In the study of Nardo et al., LSTV prevalence was found to be 11.1% in female patients and 28.1% in male patients ($p<0.001$) [17]. Similarly, in the study of Uçar et al., LSTV prevalence was found to be 17% in female patients and 20.9% in male patients ($p=0.002$) [16]. However, Tang et al. did not find a significant difference in LSTV prevalence between female and male patients [7]. Likewise, in our study, we did not find a significant difference in LSTV prevalence between female and male patients.

In a study of 534 patients with lumbar MRIs, Lee et al., reported that CA level was at the T12-L1 intervertebral disc level in 34% of the cases. They also reported that it was most commonly observed in the upper half of the L1 vertebrae in the lumbarization group and in the lower half of the T12 vertebrae in the sacralization group. There was also a statistically significant difference between these three groups ($p <0.01$) [14]. In this study and in our study, the celiac artery was found to be lower in the lumbarized group and higher in the sacralized group compared to the normalgroup.

In our study, the CA ostium was most commonly observed in the second region (50.6%) between the line passing through the middle of the T12 vertebra corpus and the T12-L1 intervertebral disc space, followed by the 1st region (30.2%) which is between the line passing through the T11-T12 intervertebral disc space and the middle of the T12 vertebra corpus. In 80% of cases, the

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CA was observed at the T12 vertebral body level. CA ostium levels were significantly different between LSTV and non-LSTV cases. In lumbarized S1 cases, CA ostium levels were observed in the lower vertebral regions compared to cases without LSTV and sacralized L5. In cases of sacralized L5, it was located in the upper vertebral region compared to the non-LSTV group.

Lee et al., reported that 34% of SMA cases were observed in the upper half of the L1 vertebrae in their study. It was also reported that 73.8% of all cases were located in the T12-L1 intervertebral disc and the upper half of L1. They noted that the most frequent area where it was located was the lower half of the L1 vertebra (47.1%) in the lumbarization group and at the level of T12-L1 intervertebral disc (35.1%) in the sacralization group. There was also a significant difference between these three groups ($p < 0.01$) [14]. In aTokgöz et al. study performed with 1049 cases, SMA was observed at the level of the L1 vertebral corpus in 55.1% of non-LSTV cases. It was noted that 58.8% of the lumbarization group was found at the L1 vertebral body level, 28.5% at the L1-L2 intervertebral disc level, and 42.9% of the sacralization group at the level of the T12 vertebral corpus. A significant difference was found in the comparison of these three groups [15].

In our study, the SMA ostium was most frequently observed in the third region (52.5%). In 27.5% of the cases, it was observed in the second region. SMA levels were significantly different in the groups with and without LSTV. SMA ostium levels in lumbarized S1 cases were observed in the lower vertebral regions compared to cases without LSTV and sacralization L5. In the case of sacralized L5, it was located in the upper vertebral region compared to the non-LSTV group.

Vascular structures can be substituted for transitional vertebrae when vertebral numbering has to be performed without whole spinal radiographs and cervicothoracic counters. A higher than expected localization of vascular structures may be a sacralization; lower localization may be an indication of the presence of lumbarization. However, the output levels of CA and SMA can not be reliably used in vertebral numbering because of their wide distribution and their differentiation by lumbarization or sacralization with LSTV presence.

To conclude, correct vertebral numbering is undoubtedly necessary to prevent errors which can occur in vertebral surgery or interventional procedures. Implementing anatomical indicators for this purpose does not seem to be efficient. In the light of our findings, we recommend obtaining whole spinal graphs or sagittal counter images before procedures and interventions that require vertebral numbering.

Compliance with Ethical Standards

Ethical Approval: This study was approved by the Marmara University School of Medicine Ethics Committee (approval number: 09.2015.354).

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Conflict of Interest: The authors have no potential conflicts to declare.

Authors' Contributions: EB and FB: Conceptualization, EB and IHS: Data collection, EB and FB: Data analysis, EB and FB: Investigation, FB: Supervision, EB, IHS and FB: Writing original draft, EB and IHS: Writing – Review and editing. All authors read and approved the final version of the article.

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Delirium and geriatric syndromes in hospitalized older patients: Results from World Delirium Awareness Day

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ABSTRACT

Objective: To determine the point prevalence of delirium and the associated risk factors in geriatric inpatients.

Patients and Methods: Sixty-two hospitalized patients aged 60 years and over were recruited. The Mini Nutritional Assessment-Short Form (MNA-SF), the FRAIL scale, Katz Activities of Daily Living (ADL), and Lawton-Brody Instrumental ADL (IADL) questionnaires were administered. A delirium evaluation test (Confusion Assessment Method-CAM) was performed for diagnosing delirium. Mortality was evaluated one month after the index date.

Results: The median age was 71.5 (range, 60-96) years. Delirium was detected in 29% of the patients. Frailty and dementia were associated with delirium ($p<0.001$ and $p=0.001$; respectively). Polypharmacy, indwelling urinary catheter, and low albumin were also related to delirium ($p=0.025$, $p=0.007$, and $p=0.002$; respectively). Age over 70 years, low Katz ADL and low MNA-SF scores were found to be independently associated with delirium in multivariate regression analysis models. The median hospitalization time was longer in the delirium group ($p=0.029$). Survival analysis at one month showed no significant difference between the delirium and non-delirium groups.

Conclusion: Age over 70 years, impaired functionality in ADL and malnutrition were independently associated with delirium.

Keywords: Delirium, Functionality, Geriatrics, Geriatric syndromes, Malnutrition

1. INTRODUCTION

Delirium is a neuropsychiatric disorder characterized by disturbances in attention, orientation and cognition, often triggered by stressors such as medical causes, pain and/or medication [1]. Although, delirium can be seen at all ages, children and older adults have the highest risk. The prevalence of delirium varies between 9% and 89%, depending on the sample and the hospital department; the incidence ranges from 18% to 35% in internal medicine and geriatrics clinics [2]. Delirium is associated with increased mortality, prolonged hospital stay, progression of dementia, impaired quality of life, and increased health care costs [3-6]. Delirium screening has been accepted as an important quality indicator for geriatric care in many countries around the world and delirium prevention interventions have become an important part of geriatric patient care programs [7, 8].

Delirium is a partially preventable syndrome. Unfortunately, due to its fluctuating course and diverse symptoms, its diagnosis is often delayed or missed [9]. Early recognition of patients at risk of delirium development may enable preventive action, thereby reducing the associated mortality. The aim of this study was to determine delirium prevalence, associated risk factors, and mortality rates in hospitalized older adults. Our secondary objective was to raise awareness about delirium with the point prevalence study we conducted on March 13th, World Delirium Awareness Day.

2. PATIENTS and METHODS

Study Design and Participants

The research was conducted on the index date of March 13th, World Delirium Awareness Day, to determine the point prevalence of delirium in the internal medicine clinic of a university hospital. The study sample consisted of patients aged 60 years and over,

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who were hospitalized in an internal medicine clinic for more than 24 hours. Exclusion criteria were coma, end of life status, and refusal of consent. Sixty-two (26 women, 36 men) eligible patients were recruited. All data were collected from the patients themselves or their first-degree relatives, the hospital electronic data system, and patient records. Written informed consent was obtained from all participants. For patients who were unable to give informed consent, written informed consent was provided by a proxy on behalf of the patient. The trial protocol was approved by Clinical Research Ethics Committee of Marmara University, School of Medicine (Protocol code: 09.2019.273).

Demographic information including age, sex, height, weight and comorbidities were recorded. Medication history was obtained from patients' medical records. The Mini Nutritional Assessment Short Form (MNA-SF) [10, 11], Katz Activities of Daily Living (ADL) and Lawton-Brody Instrumental Activities of Daily Living (IADL) [12, 13] were administered to evaluate the patients' nutritional and functional status. The MNA-SF is a screening tool scored out of 14 points. An MNA-SF score of 0-7 indicates malnutrition, and a score of 8-11 indicates malnutrition risk. Functionality was evaluated using the six-item Katz ADL scores and eight – item Lawton-Brody IADL scores. The scores for each item were determined as 1, 2, and 3 if the patient was totally dependent, partially dependent, and independent in carrying out the related activity, respectively. For the ADL, 6, 7-12 and 13-18 points, and for the IADL, 8, 9-16 and 17-24 points correspond to dependency, partial dependency, and independency, respectively.

Possible risk factors for delirium were evaluated including hearing impairment (hearing aid use), visual impairment (use of glasses), polypharmacy (five or more medications) [14], number of medications prescribed, presence of a urinary catheter, presence of a peripheral-central vein catheter, presence of nasogastric (NG)/nasoduodenal (ND) feeding tubes/ percutaneous endoscopic gastrostomy (PEG), and physical restraints. To evaluate hyponatremia, kidney damage, anemia, and inflammation, serum sodium, creatinine, hemoglobin, and C-reactive protein (CRP) values were recorded, respectively.

Frailty was assessed using the FRAIL scale, which consists of five questions on Fatigue, Resistance, Ambulation, Illness, and Loss of Weight. The FRAIL scale scores range from 0 to 5, where 3 to 5 represent frailty and 1 to 2 represent pre-frailty [15].

Patients were screened for delirium using the Confusion Assessment Method (CAM) on the index date [16]. CAM consists of four features: 1) mental disorder of acute onset or fluctuating course, 2) disturbance of attention, 3) disorganized thinking, and 4) altered consciousness. To diagnose delirium, features 1, 2 and either 3 or 4 must be present.

Mortality data were obtained from the "Ministry of Health-Death Reporting System" one month after the index date.

Statistical Analysis

The demographic and baseline characteristics of the subjects were summarized using mean and standard deviation (SD0 (or median and minimum-maximum values for non – normally distributed variables) if the variables were continuous, or frequencies and percentages if the variables were categorical. Subjects with and without delirium were compared using Student's t-test for continuous variables with normal distribution or the Mann-Whitney U test for those without. The consistency of the continuous data to normal distribution was evaluated using the Kolmogorov-Smirnov/Shapiro-Wilk tests. The Chi-square test or Fischer's exact test was used to compare categorical variables. Multivariate logistic regression analysis was used to evaluate the relationship between delirium and variables that reached statistical significance in univariate logistic regression analysis such as Katz ADL, MNA-SF, the presence of a urinary catheter, advanced age, and the number of drugs used. Multicollinearity was checked among parameters using Pearson's, Spearman's or Kendall's tau-b correlation analyses. Finally, survival analysis was performed using the Kaplan Meier test one month after the index date. All tests were two-sided and statistical significance was set at p=0.05. All statistical tests were performed using the IBM Statistical Package for the Social Sciences (SPSS) Version 22.0 software package.

3. RESULTS

A total of 62 patients were included in the study, 36 (58.1%) were male and 26 (41.9%) were female (Table I). The median age of patients was 71.5 (range, 60-96) years.

Table I. *Sociodemographic characteristics (n=62)*

Variables	Values
Sex, n (%)	
Female	26 (41.9)
Male	36 (58.1)
Age, median (min-max)	71.5 (60-96)
Marital status, n (%)	
Married	36 (58.1)
Widow/Divorced/Separated	24 (38.7)
Single	2 (3.2)
Education, n (%)	
Illiterate	20 (32.3)
Primary school	30 (48.4)
Secondary school	3 (4.8)
High school	5 (8.1)
University	4 (6.5)
Residency status, n (%)	
Home with family members	58 (93.5)
Nursing homes	4 (6.5)
Smoking, n (%)	
Active smoker	2 (3.2)
Quit smoking	32 (51.6)
Nonsmoker	28 (45.2)

The medical characteristics, comorbidities, diagnoses, and laboratory findings of the patients on the index day are shown in Supplementary Tables I and II.

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Table II. *Relationship between delirium and frailty*

	Delirium n=18 (29%)	No delirium n=44 (71%)	p value
Frailty, n (%)			0.000^
Pre-frail (FRAIL score 1-2)	0 (0)	21 (47.7)	
Frail (FRAIL score>3)	18 (100)	23 (52.3)	

^ *Fischer's exact test*

Delirium was detected in 29% (n=18) of the patients using CAM. 72% (n=13) of the patients with delirium had the hypoactive subtype. Patients with delirium were significantly older than those without delirium (76 (range, 61-96) years vs. 69 (range, 60-90) years; p=0.020). Serum albumin levels were significantly lower in patients with delirium (2.5 (range, 1.8-3.3) g/L vs 3.1 (range, 2.4-4.4) g/L; p=0.002). Delirium was detected in all five (27.8%) patients with dementia. Dementia was found to be the only comorbidity associated with delirium (p=0.001). Hypertension, diabetes mellitus and malignancies were the three most common comorbid conditions (Supplementary Table I).

Table III. *Relationship between delirium and other geriatric syndromes*

	Delirium n=18 (29%)	No delirium n=44 (71%)	p value
MNA-SF score, mean (SD)	**4.6 (±2.4)**	**8.2 (± 2.8)**	**0.000&**
Nutritional status, n (%)			**0.004#**
Normal nutritional status (MNA-SF score 12-14)	0 (0)	7 (15.9)	
At risk of malnutrition (MNA-SF score 8-11)	2 (11.1)	18 (40.9)	
Malnourished (MNA-SF score 0-7)	16 (88.9)	19 (43.2)	
Katz ADL score, median (min-max)	**7 (6-18)**	**17 (8-18)**	**0.000+**
Functional status according to Katz score, n (%)			**0.000#**
Severe dependency (0-6)	9 (50)	0 (0)	
Mild dependency (7-12)	6 (33.3)	14 (31.8)	
Independency (13-18)	3 (16.7)	30 (68.2)	
Lawton IADL score, median (min-max)	**9 (8-19)**	**16 (8-24)**	**0.000+**
Functional status according to Lawton score, n (%)			**0.000#**
Severe dependency (0-8)	8 (44.4)	1 (2.3)	
Mild dependency (9-16)	9 (50)	22 (50)	
Independency (17-24)	1 (5.6)	21 (47.7)	

MNA-SF: Mini nutritional assessment short form, ADL: Activities of daily living,

IADL: Instrumental activities of daily living, SD: Standard deviation & Student t test, + Mann Whitney U test, #Pearson chi square

Delirium was associated with old age, defined as age over 70 years (p=0.030). Patients with delirium were treated with a higher number of drugs (11 vs 9; p=0.025). Antipsychotics (p=0.006) and nutritional support products (p<0.001) were more commonly used among patients with delirium. There was no significant difference in terms of other drugs (p>0.05). Indwelling urinary catheter and delirium were also significantly associated (p=0.007).

Our study sample consisted only of pre-frail and frail patients. All patients with delirium were frail (n=18, 100%) and frailty was strongly associated with delirium (p<0.001) (Table II). Patients with delirium had significantly lower MNA-SF (4.6 vs. 8.2; p<0.001), Katz ADL (7 vs. 17; p<0.001) and Lawton IADL (9 vs. 16; p<0.001) scores (Table III).

Multivariate regression analysis was performed to determine independent risk factors for delirium. Variables with statistical significance in univariate analysis or univariate logistic regression analysis (Table IV) such as age over 70 years, presence of an indwelling urinary catheter, the number of drugs used, serum albumin level, Katz ADL score, Lawton IADL score, MNA-SF score, and frailty were reevaluated using multivariate regression analysis. Frailty, Katz ADL scores, and Lawton IADL scores were added individually and consecutively in three different regression models (Table V) because of multicollinearity. Old age was independently associated with delirium in all models (OR: 1.095, 95% CI: [0.011-0.827]; p=0.033 in Model 3). Low Katz ADL score (OR: 0.770, 95% CI: [0.602-0.985]; p=0.037) and low MNA-SF score (OR: 0.583, 95% CI: [0.357-0.951]; p=0.031) were also independently associated with delirium (Table V).

Table IV. *Variables associated with delirium according to univariate logistic regression analysis*

Variables	OR	CI 95%	p value
Age	1.093	1.016-1.175	0.17
Age>70 years	0.261	0.704-0.919	0.036
Number of drugs	1.179	1.013-1.372	0.033
IUC	0.210	0.065-0.679	0.009
Albumin	0.131	0.032-0.536	0.005
Katz ADL	0.679	0.565-0.816	0.000
Lawton IADL	0.661	0.504-0.867	0.003
MNA-SF	0.598	0.449-0.797	0.000

OR: odds ratio, CI: confidence interval, IUC: indwelling urinary catheter, ADL: activities of daily living, IADL: instrumental activities of daily living, MNA-SF: mini nutritional assessment short form.

Table V. *Multivariate regression analysis: Association between delirium and increased age, malnutrition and lower functionality in activities of daily living after adjusting for confounders*

	Model	Model 2	Model 3
	Odds ratios [95 % confidence interval]		
Age ≥70 years	**0.124 [0.017-0.904]**[1a]	**0.087 [0.10-0.790]** [2a]	**1.095[0.011-0.827]**[3a]
Number of drugs	1.202 [0.950-1.520]	1.146 [0.907-1.448]	1.173[0. 927-1.483]
IUC	0.452 [0.091-2.238]	0.578[0.100-3.339]	0.550[0.098-3.073]
Albumin	0.528 [0.077-3.624]	0.791 [0.094-6.657]	0.689[0.081-5.854]
MNA-SF	**0.583 [0.357-0.951]** [1b]	**0.560 [0.331-0.948]** [2b]	**0.560[0.328-0.957]** [3b]
Frailty	0.000 [-]		
Katz ADL		**0.770 [0.602-0.985]**[2c]	
Lawton IADL			0.776[0.588-1.024]

OR odds ratio, CI confidence interval, IUC indwelling urinary catheter, ADL activities of daily living, IADL instrumental activities of daily living, MNA-SF mini nutritional assessment short form. 1ap=0.039; 1bp=0.031, 2ap=0.030, 2bp=0.031, 2cp=0.037, 3ap=0.033, 3bp=0.033

Patients were evaluated in terms of total hospital stay and mortality one month after the index day. A total of 38.9% (n = 7) of the patients with delirium and 13.6% (n = 6) of the patients without delirium died within one month (in our hospital or another center) (p=0.04) (Table VI). According to the results of the survival analysis performed using the Kaplan – Meier method, the mean survival time in patients with delirium was 53±9.65 (34.09-71.91) (median survival time (days) + SE [95% CI]). For patients without delirium, the mean survival time was 56+10.44 (35.54-76.46). There was no statistically significant difference (p=0.598) (Table VII). The median hospitalization time was longer for patients with delirium (29 (range, 13-80) vs. 18 (range, 5-71) days; p=0.029).

Table VI. *Mortality of patients with delirium*

	Delirium n=18, 29%	No delirium n=44, 71%	p value
Mortality within a month, n (%)	**7 (38.9)**	**6 (13.6)**	**0.040**^

^*Fischer's exact test*

Table VII. *Kaplan Meier survival analysis*

	Median (days)	SE	CI 95%
Patients with delirium (n=18)	53	9.65	34.09-71.91
Patients without delirium (n=44)	56	10.44	35.54-76.46

SE: standard error, CI: confidence interval

4. DISCUSSION

In this study, we investigated delirium risk factors in hospitalized patients aged 60 years and over. All patients included in the study were either pre-frail or frail, in line with other studies in geriatric inpatients [17]. Our delirium rate was 29%, which was also consistent with a previous study [18]. All patients with delirium were frail. Similar results have been reported in the literature, indicating a strong association between frailty – in comparison with being pre-frail – and delirium [19-21]. Frailty is a geriatric syndrome caused by a decrease in the individual's response to stress factors. It is associated with increased falls, long-term hospitalization, sarcopenia, delirium, and even mortality [22]. Frailty occurs in one-third of older adults when they are hospitalized. Even if the patient is treated successfully, frailty persists and increases mortality. Delirium and frailty are common geriatric syndromes with similar risks and outcomes in the hospitalized older adults [20, 23]. Delirium may delay physical and cognitive healing, both of which lead to frailty [19]. At the cellular level, microglial cells in the brain, which respond to inflammation and injury, become hyper-sensitive to stimuli in frail individuals, causing neuronal damage [24]. Hyper-responsive microglia also play a significant role in the pathophysiology of delirium, linking the two geriatric syndromes together [25].

In line with the literature, we found dementia and older age (over 70 years) to be strongly associated with delirium [26, 27]. There was a statistically significant difference between patients with and without delirium concerning their ages. Older age remained as an independent risk factor for delirium in multivariate logistic regression analysis. This relationship can be explained by age-related microvascular changes in the brain, which render the individual more susceptible to neurocognitive disorders. The pre-existing neurodegeneration of dementia also creates a predisposition to delirium. In a meta-analysis examining the association between delirium and dementia, delirium superimposed on dementia was observed at a rate of 22-89% [28]. In our study, delirium developed in all five patients who had dementia. Common mechanisms underlying the pathogenesis of delirium and cognitive impairment, which include inflammation, atherosclerosis, and malnutrition, may account for this strong association [29].

Physical restraints, another risk factor for delirium, have been reported to increase delirium risk up to 4.5 times [2, 30]. In our study, delirium was detected in all physically restrained patients. It is of note that 50% of these patients were on antipsychotic medication. Therefore, a reverse causality between delirium and physical restraints is also possible.

A cohort study was conducted by Inouye et al. to develop a model that could predict delirium development and they found five independent precipitating factors: physical restraints, the

addition of more than three medications, urinary catheterization, malnutrition, and any iatrogenic events [31]. According to this study, the presence of a urinary catheter was found to increase delirium risk by 2.4-fold [31]. Bo et al.'s study, which consisted of 1867 hospitalized patients and 1464 nursing home residents, showed that urinary catheterization was independently associated with delirium in hospitalized patients [26]. In accordance with previous studies, we found that the presence of a urinary catheter was associated with delirium. The high rate of urinary catheter use in our clinic may be explained by the multiple comorbidities of hospitalized patients. To prevent delirium, the Hospital Elder Life Program (HELP) and National Institute for Health and Care Excellence (NICE) guidelines recommend avoiding unnecessary urinary catheter use [32, 33]. Urinary catheterization was not an independent risk factor in our study, which may be due to our small sample size.

Studies have shown that polypharmacy is a risk factor for delirium in geriatrics [24]. In the study conducted by Hein et al., the average number of drugs used by 410 older patients in an acute geriatric ward admission was 6.21, where 69% of patients with polypharmacy developed delirium. As a result, polypharmacy was found to be an independent risk factor for delirium in older patients, regardless of the type of medication [34]. Similar to previous studies, we found that patients with delirium were on a higher number of medications [2]. However, the number of drugs was not independently associated with delirium. Contrary to previous studies, we had a higher polypharmacy rate, possibly because the study was conducted in a tertiary healthcare center.

Some drug groups including anticholinergics, dopaminergics, sedative-hypnotics, narcotics, H2 receptor antagonists, antihistamines, fluoroquinolones and analgesics are considered more deliriogenic than others. Among these medications, antipsychotics are the most controversial. Despite their use in delirium treatment, some studies suggest that antipsychotics are deliriogenic [35]. In our study, all patients receiving antipsychotics had delirium. Enteral and parenteral nutrition products were also used more commonly in patients with delirium. This finding is in accordance with studies showing that malnutrition is a risk factor for delirium because nutritional products are mostly used in poor nutritional status [36]. HELP has similarly demonstrated that avoiding malnutrition is one of the effective non – pharmacologic interventions for delirium prevention [37, 38]. As mentioned before, malnutrition is involved in the pathogenesis of delirium. Mazzola et al., revealed that malnutrition risk and malnutrition were independent determinants of postoperative delirium in patients undergoing hip surgery [39]. MNA-SF is a test with 97.9% sensitivity, 100% specificity, and 98.7% diagnostic accuracy [11, 40]. In our study, malnutrition was detected in 88.9% and malnutrition risk in 11.1% of patients using MNA-SF. Multivariate regression analysis adjusted for old age and functional impairment showed that delirium was more likely in patients with low MNA-SF scores. Serum albumin, a laboratory indicator of nutritional status, was also lower in patients with delirium.

The Katz ADL and Lawton IADL are indices used to assess functional status in older adults [12, 24]. In a cohort study of 374 patients aged over 65 years, Carrasco et al., found that delirium was independently associated with low functional status as determined with the Barthel index [41]. In a meta-analysis performed by Watt et al. after elective surgery, impairment in ADL, and impairment in IADL were predictors of delirium [42]. In our study, multivariate regression analysis adjusted for low MNA-SF score, older age, and polypharmacy showed that delirium was more likely in patients with low ADL scores. On the other hand, delirium itself may also cause ADL and IADL impairment.

It is also of note that 72% of the patients with delirium had the hypoactive subtype. Hypoactive delirium is more prevalent and is associated with a greater risk for mortality compared to the hyperactive subtype [43]. This may be due to the fact that unlike the hyperactive subtype, hypoactive delirium tends to go unnoticed. It may also be that patients who are more frail at baseline are unable to present with signs of psychomotor agitation. Thus, clinicians who care for older adults should be on the lookout for signs of hypoactive delirium, which include sleepy appearance, slow response or lack of communication.

Previous studies reported an association between delirium and mortality. In Adamis et al.'s cohort study of 164 patients, delirium was not related to in-hospital and 6-month mortality [18]. Likewise, in a review by Hamillton et al. on postoperative delirium, delirium was not associated with mortality in studies that controlled for confounders [44]. In contrast with this information, some studies show that delirium is effective in predicting 3 or even 12-month mortality [20, 45-48]. We evaluated mortality 30 days after the index date using an electronic database. Although mortality rates were found to be significantly higher in patients with delirium, the same significance was not reached in Kruskal-Wallis survival analysis. The results of our study are compatible with studies that found no relationship between delirium and mortality, though our short follow-up period may also be accountable.

Additional healthcare costs are another detrimental effect of delirium [49]. Most health expenses related to delirium are due to prolonged hospitalization of patients. In Siddiqi et al.'s review of 42 cohort studies, delirium was associated with longer hospital stay [8], which is in keeping with our results.

Our study has some limitations. First, the sample group was relatively small and the study was conducted in a single center. Thus, our findings cannot be generalized to the entire population. Second, patients were evaluated at a single point in time, which may have resulted in underdiagnosis of delirium. To overcome this obstacle, a delirium chart can be created for the entire healthcare team, including night-shift healthcare workers. Third, our study group consisted only of pre-frail and frail patients, as expected of a tertiary healthcare institution. Therefore, the difference in delirium prevalence between non-frail and frail patients could not be accurately investigated. Finally, Cox regression analysis could not be performed because mortality was evaluated one month after the index date. Multicenter studies with longer follow – up periods

may reveal more accurate associations between delirium and mortality.

Our study also has several strengths. To the best of our knowledge, this is the first point prevalence study of delirium in Turkey using CAM. World Delirium Awareness Day was chosen as the index date of our study to draw attention to delirium. Moreover, geriatric syndromes including frailty, malnutrition, polypharmacy, and functional impairment were assessed simultaneously.

With the advent of the COVID-19 pandemic, where older adults have elevated rates of hospitalization, delirium awareness has become more important than ever. Our study revealed that delirium is independently associated with older age, malnutrition, and functional impairment in hospitalized older patients. We recommend that delirium prevention strategies should be developed to minimize modifiable risk factors. High-risk patients should be screened for delirium at regular intervals and information pamphlets should be given to caregivers, as well as healthcare professionals.

Compliance with the Ethical Standards

Ethical Approval: The study was approved by Clinical Research Ethics Committee of Marmara University, School of Medicine (Protocol code: 09.2019.273). Written informed consent was obtained from all participants. For patients who were unable to give informed consent, written informed consent was provided by a proxy on behalf of the patient.

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Supplementary Table I. *Medical characteristics of patients (n=62)*

Variables	Values
BMI, median (min-max)	24.8 (15.6-39.1)
Diagnosis, n (%)	
Malignancy research	7 (11.3)
Respiratory diseases	21 (33.9)
Gastrointestinal system diseases	5 (8.1)
Acute kidney injury	10 (16.1)
Infectious diseases	5 (8.1)
Any prior tumor	9 (14.5)
Others	5 (8.1)
Comorbidities, n (%)	
Follow up after intensive care stay	13 (21)
Dementia	5 (8.1)
Malignancies	29 (46.8)
COPD	19 (30.6)
Pulmonary embolism	11 (17.7)
Diabetes	21 (35.5)
Chronic kidney disease	13 (21)
Hemodialysis	6 (9.7)
Coronary artery disease	17 (27.4)
Heart failure	11 (17.7)
Atrial fibrillation	11 (17.7)
Hypertension	31 (50)
Hypothyroidism	6 (9.7)
Others	8 (12.9)

BMI: body mass index; COPD: chronic obstructive pulmonary disease

Supplementary Table II. *Laboratory findings of patients (n=62)*

Variable	Values
Creatinine, median (mg/dl) (min-max)	0.83 (0.34-5.38)
GFR, median (ml/min) (Cockroft) (min-max)	69 (10-186)
Hemoglobin, median (g/dl) (min-max)	10.1 (7-16.3)
CRP, median (mg/L) (min-max)	26.1(3.1-248)
Sodium, median (mEq/L) (min-max)	137 (123-146)
Albumin, median (g/L) (min-max)	2.8 (1.8-4.4)

GFR: glomerular filtration rate, CRP: C-reactive serum protein

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Prognostic value of the lactate–albumin difference for predicting in-hospital mortality in critically ill patients with sepsis

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ABSTRACT

Objective: To evaluate the prognostic performance of the lactate–albumin difference (LAD), maximum lactate levels, and the Sequential Organ Failure Assessment (SOFA) score taken on the first day in critically ill patients with sepsis, on in-hospital mortality and 90-day survival.

Patients and Methods: Data from the Medical Information Mart for Intensive Care III (MIMIC III) version 1.4 were evaluated retrospectively. The first day data of adult patients with sepsis diagnosed according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria were recorded. The effectiveness of all diagnostic modalities on admission was analyzed to predict in-hospital mortality and 90-day survival.

Results: In-hospital mortality was 20.3% among the 2270 patients included in this study. The area below the receiver operating characteristic curve (AUC) value of the LAD was higher than lactate for predicting mortality (AUC, 0.691; 95% confidence interval [CI], 0.663–0.718; $p< 0.01$, and AUC, 0.675; 95% CI, 0.646–0.703; $p< 0.01$, respectively), and the AUC of SOFA score was the highest (AUC, 0.716; 95% CI, 0.663–0.718). The optimal cutoff of LAD was 0.7.

Conclusion: In addition to its easy and simple calculability relative to the SOFA, the prognostic performance of LAD was superior to maximum lactate levels for predicting in-hospital mortality and 90-day survival in adult patients with sepsis.

Keywords: Lactate-albumin difference, Lactate, Sepsis, In-hospital mortality, Survival

1. INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. In sepsis, the primary cause of death is infection, which should be recognized and treated promptly. Based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) definitions, the mortality of patients with sepsis and septic shock in low – and middle-income countries is 35.5% and 75.6%, respectively [2,3]. The high mortality rate necessitates using predictive biomarkers to early detection of sepsis and after the efficacy of treatment regimens.

Hypoxia, hypoperfusion, organ dysfunctions, sepsis, and several conditions increase serum lactate levels [4,5]. In-hospital mortality predictors and prognostic indices are used in unselected intensive care unit (ICU) patients and patients with sepsis. The predictive ability of lactate concentration is comparable with the other indices [6,7].

Albumin is one of the negative acute-phase proteins and has an important role in severe sepsis and inflammatory processes; having a low albumin level is associated with increased mortality.

Lactate and albumin levels are used independently in predicting in-hospital mortality in sepsis; more studies were conducted using their combination to further increase the predictive value.

An increase in lactate and a decrease in albumin levels are associated with high mortality risk; therefore, we hypothesized that lactate–albumin difference (LAD) might be a stronger predictor than these parameters alone. The prognostic performance of the LAD, maximum lactate levels, and initial values of the Sequential Organ Failure Assessment (SOFA)

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scores [8] on the first admission to ICU for predicting in-hospital mortality in patients with sepsis were evaluated.

2. PATIENTS and METHODS

In this study, Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC III) version 1.4 data between 2001 and 2012 were retrospectively evaluated. Deidentified data of more than 40,000 ICU patients can be found in the MIMIC III database [9]. The institutional review boards of the Beth Israel Deaconess Medical Center (protocol 2001-P-001699/14) and Massachusetts Institute of Technology (protocol 040.300.0206) approved the use of MIMIC III for research and granted waiver of informed consent.

Cohort Selection

Data were extracted from MIMIC III using the Structured Query Language scripts [9]. All patients in the MIMIC III were screened, and the first ICU admissions of patients at the age of ≥16 years were selected. Patients at the age of > 89 years or > 1 ICU stay; post-cardiac, vascular, or thoracic surgery patients; patients with late diagnoses; patients without available documentation or with missing data; and patients with pregnancy-related diagnoses were excluded.

Statistical Analysis

Means with standard deviations or medians with interquartile ranges were used to describe patient characteristics. Total numbers and percentages were used to present categorical variables. Continuous variables were analyzed using the Wilcoxon rank-sum tests, and categorical variables were analyzed using Chi-square tests, as appropriate.

Univariable and multivariable logistic regression models were used to analyze the association between in-hospital mortality and the maximum lactate, minimum albumin, and LAD values at admission, and odds ratios were calculated.

We analyzed the capacity of all diagnostic modalities (SOFA, maximum lactate, minimum albumin, and LAD) at admission to predict in-hospital mortality using the area under the receiver operating characteristic curve (AUCs) with 95% confidence intervals (CIs). The Youden method was used to determine the optimal cutoff value [10]. Furthermore, sensitivity and specificity were determined at this value. The 90-day survival curves from the first day of ICU admission were obtained from Kaplan–Meier estimation.

P< 0.05 was considered statistically significant. RStudio (version 1.2.5033) was used for all statistical analyses [11].

3. RESULTS

Patients who met the exclusion criteria (n = 40,111) of 61532 patients in the ICUs were excluded from the study. After excluding patients with missing and outline initial arterial lactate and venous albumin data (n = 7424), 3176 patients were evaluated for the diagnosis of sepsis based on the Sepsis-3 criteria, and finally, 2270 patients were included in the study. They were divided into 2 groups, namely, survived discharged group (survivors group, n = 1809) and demised in-hospital group (nonsurvivors group, n = 461). The in-hospital mortality rate (20.3%) for the study group is presented in Figure 1.

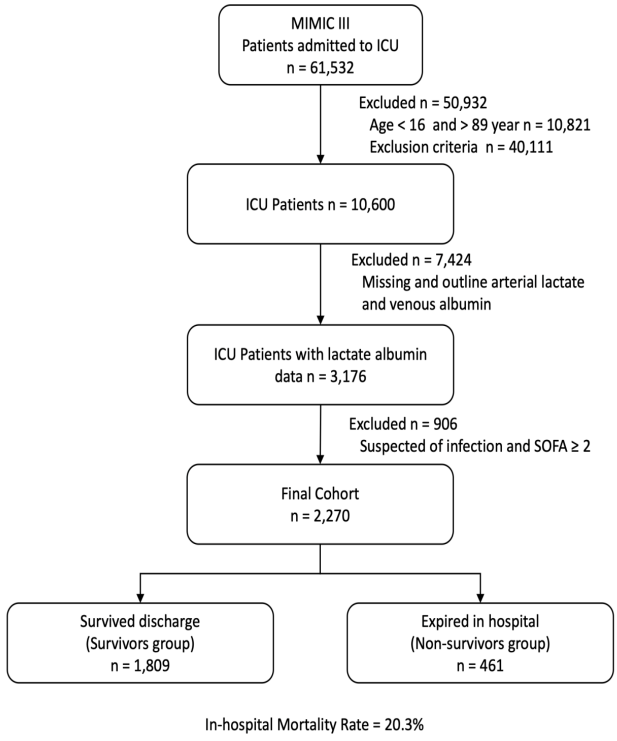

Figure 1. *A flowchart of patient inclusion and exclusion*

The demographic characteristics of the study cohort are presented in Table I. The nonsurvivors, compared with survivors were older (p< 0.001). SOFA score (first day) (p<0.001),Elixhauser comorbidity score (p < 0.001) [12], Oxford Acute Severity of Illness Score

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Table I. *Patients' baseline demographic characteristics*

Characteristics	Overall (n = 2270) [1]	Survivors (n = 1809 [80%][1])	Nonsurvivors (n = 461 [20%][1])	p value[2]
Age, (y)	63 (52-76)	62 (50-74)	69 (56-80)	< 0.001
Male, n (%)	1312 (58%)	1039 (57%)	273 (59%)	0.5
BMI, (kg/m2)	28 (24-33)	28 (24-33)	27 (24-32)	0.5
SOFA (first day)	6 (4-8)	5 (4-7)	8 (5-12)	< 0.001
Admission type,n (%)				0.11
Elective	67 (3.0%)	60 (3.3%)	7 (1.5%)	
Emergency	2170 (96%)	1724 (95%)	446 (97%)	
Urgent	33 (1.5%)	25 (1.4%)	8 (1.7%)	
Initially admitted service, n (%)				0.10
CMED	189 (8.3%)	143 (7.9%)	46 (10.0%)	
MED	1459 (64%)	1157 (64%)	302 (66%)	
NMED	76 (3.3%)	60 (3.3%)	16 (3.5%)	
NSURG	119 (5.2%)	89 (4.9%)	30 (6.5%)	
SURG	229 (10%)	197 (11%)	32 (6.9%)	
TRAUM	103 (4.5%)	86 (4.8%)	17 (3.7%)	
Other services	95 (4.2%)	77 (4.3%)	18 (3.9%)	
Elixhauser comorbidity score	4 (0-9)	4 (0-9)	7 (3-12)	< 0.001
Mechanical ventilation, n (%)	1271 (56%)	935 (52%)	336 (73%)	< 0.001
Metastatic cancer	144 (6.3%)	92 (5.1%)	52 (11%)	< 0.001
Length of hospital stay, (day)	8 (5-14)	9 (5-15)	5 (2-11)	< 0.001
Length of ICU stay, (day)	3.0 (1.7-6.7)	3.0 (1.8-6.3)	3.5 (1.7-7.2)	0.5
Lactate (max) (mmol/L)	2.30 (1.50-4.00)	2.20 (1.50-3.50)	3.40 (2.10-7.00)	< 0.001
Albumin (min) (mg/dL)	3.10 (2.60-3.60)	3.10 (2.60-3.60)	2.80 (2.30-3.30)	< 0.001
Lactate–albumin difference	−0.70 (−1.60-1.00)	−0.90 (−1.70-0.50)	0.70 (−0.90-4.40)	< 0.001
ICU severity score				
OASIS	35 (29-41)	33 (28-39)	42 (37-47)	< 0.001
APSIII	48 (36-64)	45 (34-59)	65 (50-84)	< 0.001
SAPSII	40 (32-52)	38 (30-48)	55 (44-67)	< 0.001

Values are taken within 24 hours of admission to the ICU 1Statistics are presented as median (interquartile range) and number (percentage).2Statistical tests performed were Wilcoxon rank-sum test and Chi-square test of independence. BMI: body mass index, SOFA: Sequential Organ Failure Assessment, CMED: coronary, MED: medical, NMED: neurological, NSURG: neurosurgical, SURG: surgical, TRAUM: trauma, ICU: Intensive Care Unit, OASIS: Oxford Acute Severity of Illness Score, APSIII: Acute Physiology and Chronic Health Evaluation III, SAPSII: Simplified Acute Physiology Score II.

(OASIS) (p< 0.001), Acute Physiology Score III (APS III) (p< 0.001), Simplified Acute Physiology Score II (SAPS II) (p< 0.001), and the percentage of mechanical ventilation p< 0.001) and metastatic cancer (p< 0.001) were higher in this group.

Table II. *Univariate and multivariate logistic regression analyses of variables potentially associated with in-hospital mortality in intensive care patients*

	Univariate binary logistic regression			Multivariate logistic regression		
Predictor	OR[1]	95% CI[1]	*P*-value	OR[1]	95% CI[1]	*P*-value
Age	1.02	1.02, 1.03	< 0.001	1.03	1.02, 1.04	< 0.001
Gender (male = 1)	1.08	0.87, 1.33	0.5	0.98	0.78, 1.25	0.9
SOFA	1.25	1.21, 1.28	< 0.001	1.17	1.13, 1.22	< 0.001
Elixhauser comorbidity score	1.07	1.05, 1.08	< 0.001	1.02	1.01, 1.04	< 0.001
Metastatic cancer	2.37	1.65, 3.38	< 0.001	2.34	1.50, 3.61	< 0.001
Mechanical ventilation	2.51	2.01, 3.16	< 0.001	1.70	1.29, 2.25	< 0.001
Admission type						
Emergency	2.22	1.08, 5.36	0.048	2.04	0.89, 5.38	0.12
Urgent	2.74	0.89, 8.62	0.077	1.48	0.41, 5.43	0.5
First service						
MED	0.81	0.57, 1.17	0.2	0.76	0.50, 1.16	0.2
NMED	0.83	0.43, 1.55	0.6	1.69	0.82, 3.38	0.14
NSURG	1.05	0.61, 1.32	0.9	2.08	1.14, 3.77	0.017
SURG	0.50	0.30, 0.83	0.007	0.30	0.17, 0.54	< 0.001
TRAUM	0.61	0.32, 1.12	0.12	0.75	0.36, 1.51	0.4
Other	0.73	0.39, 1.32	0.3	0.75	0.35, 1.54	0.4
Lactate–albumin difference	1.25	1.21, 1.29	< 0.001	1.36	1.13, 1.65	0.001
Lactate (max)	1.25	1.20, 1.29	< 0.001	0.86	0.71, 1.04	0.12
Albumin (min)	0.56	0., 0.45	< 0.001	—	—	—

[1]OR, odds ratio, CI, confidence interval; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit, BMI: body mass index, CMED: coronary, MED: medical, NMED: neurological, NSURG: neurosurgical, SURG: surgical, TRAUM: trauma, OASIS: Oxford Acute Severity of Illness Score, APSIII: Acute Physiology And Chronic Health Evaluation III, SAPSII: Simplified Acute Physiology Score II.
Values are taken within 24 hours of admission to the ICU.
The P-value of the Hosmer-Lemeshow goodness-of-fit test for the multivariate logistic regression model was 0.286, and Negelkerke was 0.330.

Survivors had a longer hospital stay (p< 0.001), but the length of ICU stay (p= 0.5) and admission types (p= 0.10) were similar.

Nonsurvivors had higher lactate p< 0.001), higher LAD (p< 0.001), and lower albumin (p< 0.001) levels than survivors. There was no difference between the distribution of the initially admitted service of patients and the groups (p= 0.10).

The analyses of variables potentially associated with in-hospital mortality are presented in Table II. The multivariate logistic regression model identified age (p< 0.001), SOFA score (p< 0.001), Elixhauser comorbidity score (p< 0.001), metastatic cancer (p< 0.001), mechanical ventilation (p< 0.001), initially

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admitted service (Neurosurgery, Surgery) (p< 0.001), and LAD (p< 0.001). The Hosmer-Lemeshow test was not significant (p= 0.286) [13], and Negelkerke was 0.330, indicating that the model adequately fits the data.

The optimal cutoff values, AUC, Youden's index, sensitivity, and specificity for SOFA score, LAD, and maximum lactate are presented in Table II.

The AUC of LAD (AUC, 0.691; 95% CI, 0.663–0.718) was larger than the maximum lactate (AUC, 0.675; 95% CI, 0.646–0.703) on the first day (Table III). The AUC of SOFA score was the largest (AUC, 0.716; 95% CI, 0.663–0.718) of these predictors (Table III).

Table III. *Cutoff value, Youden index, sensitivity, and specificity of predictors associated with in-hospital mortality*

Predictors	Cutoff value	AUC	Youden's index	Sensitivity (%)	Specificity (%)
SOFA score	8	0.716	0.3261	57.04	75.56
Lactate–albumin difference	0.7	0.691	0.2771	50.32	77.39
Lactate (max)	4.4	0.675	0.4189	41.64	82.97

SOFA: Sequential Organ Failure Assessment

The Kaplan–Meier 90-day survival curves with risk tables and 95% CIs of the LAD and SOFA scores on the first day according to the cutoff values are presented in Figure 2. When cutoff values were used, the survival curves indicated a significant difference (p< 0.001 for all)

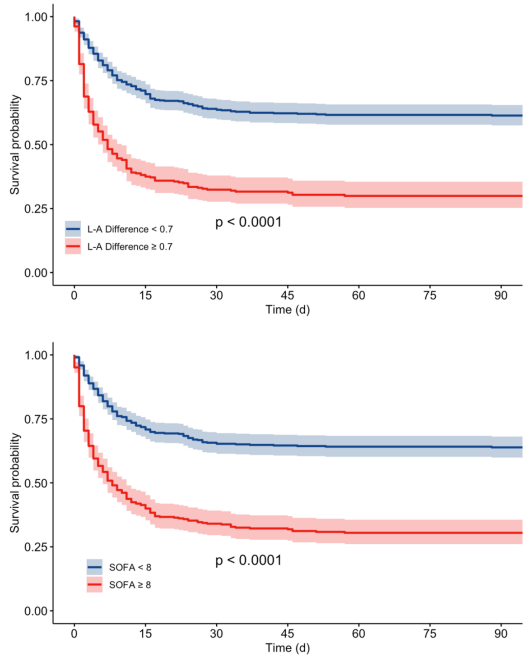

Figure 2. *Kaplan–Meier 90-day survival curves with risk tables of the lactate–albumin differences and Sequential Organ Failure Assessment score on the first day according to the cutoff values*

4. DISCUSSION

In this study, we used the first ICU admission values of critically ill adult patients with sepsis from the MIMIC III version 1.4 to evaluate the prognostic significance of LAD for in-hospital mortality. Compared with maximum lactate in predicting in-hospital mortality, LAD had a better prognostic performance in this cohort.

Increased lactate concentrations are strongly correlated with the severity of sepsis and the mortality risk at 30 days and 1 year in patients with septic shock defined by Sepsis-3 [14-16]. Numerous alterations in lactate metabolism such as factors affecting its production, that is, cellular hypoxia, shock, beta-adrenergic stimulation, factors affecting its clearance (i.e., liver dysfunction), or simply an intravenous infusion of solutions that contain lactate), may lead to hyperlactatemia [17].

Inflammatory processes may lead to a decline in albumin levels, and the existence of hypoalbuminemia may reflect inflammation. Along with the decrease in total albumin levels, the half-life of albumin is also shortened as the capillary permeability increase enhances the escape of serum albumin. Serum albumin levels are markers of the clinical state, such as malnutrition, various diseases, trauma, or organ failure and result in hypoalbuminemia [18,19]. Having excluded exogenous albumin administration, hypoalbuminemia is correlated with increased mortality in sepsis, and in addition to APACHE II, serum albumin levels can be used to predict mortality risk in community-acquired severe sepsis and septic shock [19,20].

In inflammatory states and in sepsis, serum levels of lactate increase, whereas albumin levels decrease. Knowing the actual levels of serum lactate and albumin is important in patients with sepsis, but the importance of using the difference between lactate and serum albumin in providing a variable that positively correlated with organ dysfunction and mortality is unclear. Wang et al. [21] and Lichtenauer et al. [22] studied the correlation of the lactate–albumin ratio (LAR) to organ dysfunction and mortality in patients with sepsis in the ICU and reported a strong association. However, LAD would provide a better correlation than the ratio. Recently, the prognostic value of the LAD over the LAR and maximum lactate in predicting 30-day mortality in critically ill patients was studied [23]. It revealed that LAD is an independent prognostic marker for organ dysfunction and mortality in patients with sepsis. To the best of our knowledge, this study is the first to use LAD from patients with sepsis in the ICU to evaluate in-hospital mortality. Our findings also indicate that LAD is a useful target for predicting 90-day survival in critically ill patients with sepsis; it is superior to a single lactate measurement.

It is known that lactate is important in severe sepsis and septic shock, but it is unclear whether the ratio of lactate and albumin would provide a variable that correlated positively with multiple organ dysfunction syndrome (MODS) and mortality. This study was designed to investigate the prognostic importance of LAR when lactate concentration is >4 mmol/L.

For in-hospital mortality, Casserly et al., revealed the cutoff value for lactate as > 4 mmol/L in severe sepsis or septic shock patients,

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with and without hypotension [5]. Our findings indicate that maximum lactate concentration of >4.4 mmol/L is a pertinent target in patients with sepsis and septic shock defined by Sepsis-3.

The first limitation of this study is that it uses a single institution's database and analyses retrospectively. Secondly, the final cohort may not reflect the entire cohort, owing to missing lactate and albumin data; only 3.6% of the overall MIMIC III data (2270 of 61,532) were evaluated. Finally, only patients with sepsis in the ICU were evaluated, which might have led to selection bias.

Because measuring single lactate and albumin value is simple and inexpensive compared to some of the novel tests, based on our findings that LAD has sufficiently predicted in-hospital mortality, we suggest that it can be used for screening high-risk patients. Further studies are needed for prospective validation and risk stratification.

Conclusion

The prognostic performance of LAD was superior to that of maximum lactate levels for predicting in-hospital mortality in adult patients with sepsis. In addition to its simplicity and easy calculability, LAD, relative to the SOFA score, is a better prognostic factor than maximum lactate levels. Because this work has evaluated retrospective data and the laboratory values obtained on the first day may affect results, further prospective studies with different predetermined timings of lactate and albumin values are needed on this subject.

Compliance with the Ethical Standards

Ethical Approval: The institutional review boards of the Beth Israel Deaconess Medical Center (protocol 2001-P-001699/14) and Massachusetts Institute of Technology (protocol 040.300.0206) approved the use of MIMIC III for research and granted waiver of informed consent.

Financial Support: The authors have no relevant financial information to close.

Conflict of Interest: The authors have no potential conflicts of interest to disclose

Author Contributions: GTA, MKA, PCD, RA and AK: Conceived and planned the study. They were mainly responsible for the design of the study. MKA and GTA: Collected the data,

MKA and AK: were mainly responsible for analyzing the data, GTA, MKA, PCD and RA: Wrote the first draft of the manuscript. All authors contributed to the interpretation of findings and reviewed the manuscript. GTA, MKA and AK: Reviewed the statistical analyses and made changes to the content of the manuscript. All authors have also provided intellectual contribution to the manuscript.

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Contact lens usage and health literacy among Turkish adults

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ABSTRACT

Objective: To evaluate the usage of contact lenses and health literacy among ophthalmology clinic outpatients..

Patients and Methods: This cross-sectional study was conducted on outpatients of an ophthalmology clinic between July and September 2019. The data were collected using a questionnaire that consisted of questions about sociodemographic characteristics, contact lens-related behaviors, the European Health Literacy Scale (HLS-EU) Short-Form, and the Ocular Surface Disease Index. Contact lens-related behavior was evaluated through 15 questions. $P < 0.05$ was accepted as statistically significant.

Results: In the study group 402 (54.8%) of the participants were males. The ages of the patients ranged between 18 and 75 years, with a mean (SD) of 39.20 (15.0) years. It was found that 28.4% (n = 208) of the study group participants were contact lens wearers. The health literacy level was higher in the contact lens wearers. A positive correlation was found between the scores of the HLS-EU and the answers to the contact lens-related behavior questions.

Conclusion: In this study, we found that the health literacy levels of the contact lens wearers were higher than those of the non-contact lens wearers. As the health literacy of the patients increased, the behaviors towards the correct use of contact lenses improved. It is recommended that more detailed studies be carried out in the field of health literacy with contact lens use.

Keywords: Contact lenses, Dry eye syndrome, Eye diseases, Health literacy

1. INTRODUCTION

Contact lenses are medical devices that began to be produced in the late 19th century. The main purpose for the contact lens production was to correct refractive errors. Nowadays, they are used for cosmetic and therapeutic purposes, as well as the correction of refractive errors [1, 2].

The use of contact lenses has become widespread all over the world. It is estimated that about 140 million people wore them worldwide in 2010 [3]. In the United States, it is thought that contact lens use has risen to 45 million [4]. However, the number of contact lens users is not clear in Turkey. It was reported that the number of people who do not use any devices to correct their sight, such as glasses or contact lens, is decreasing progressively; in 2016, 35.6% of individuals aged 15 years and over wore glasses or contact lenses [5].

Contact lenses are known to be very safe and effective when used properly. However, contact lens use causes many complications, such as microbic keratitis. Inadequate contact lens hygiene and failure to follow the instructions for contact lens use have been reported as the main causes of keratitis in contact lens wearers. On the other hand, the risk of other eye problems, such as dry eye syndrome, increases in contact lens users. These infectious complications, like superior limbic keratoconjunctivitis, may cause serious health problems, including vision loss. Contact lens-related complications were reported to occur at a rate of around 5% and loss of vision is 0.6 per 10,000 users. It is estimated that contact lens-related health problems cost 175 million dollars annually in the USA [6–10].

Healthy contact lens use and regular ophthalmologist check-ups are the most effective ways to prevent contact lens-related health

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problems. In addition to preventive methods, early treatment also plays a significant role in dealing with complications. With this in mind, a new concept, namely health literacy, is a leading factor that affects the health behaviors of individuals and their compliance to health advice. Health literacy covers accessing, understanding, appraising, and applying health-related information within healthcare. It is thought that having competent health literacy knowledge is an important issue in assisting contact lens users in avoiding complications [2, 11–14]. However, studies evaluating the use of contact lenses and health literacy in Turkey are limited.

The aim of this study was to evaluate the usage of contact lenses and health literacy among the Eskisehir Osmangazi University Hospital Ophthalmology Clinic outpatients.

2. PATIENTS and METHODS

This cross-sectional study was conducted on the outpatients of an ophthalmology clinic between July and September 2019.

The study was conducted in accordance with the regulations of the Eskisehir Osmangazi University Hospital Directorate and ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Eskisehir Osmangazi University with prothocol no: 25.06.2019/15. Written informed consent was obtained from all of the participants in the study.

In this study, the sample size was estimated as at least 384 participants (with a contact lens use prevalence of 50%, a 5% margin of error at a 95% confidence level). The study group consisted of 733 patients.

The data of the study was collected via a questionnaire form. The questionnaire form consisted of questions regarding sociodemographic characteristics, contact lens-related behaviors, the European Health Literacy-Q16 (HLS-EU-Q16) Scale and the Ocular Surface Disease Index (OSDI) [2,12,13,15,16]. The questionnaire forms were filled by the researchers in the waiting room of the clinic during face-to-face interviews with the participants. This process took about 20–25 min.

A 15-item questionnaire was applied to the patients about how they used their contact lenses. They were asked to answer yes or no to each question. Each correct behavior was evaluated as 1 point and a wrong behavior was evaluated as 0 points. A total of 0–15 points could be obtained from the questionnaire. As the score obtained from the questionnaire increases, the behaviors change positively.

The HLS-EU was developed by the European Health Literacy Consortium within the framework of the European Health Literacy Project, between 2009 and 2012. The HLS-EU-Q16 was developed to include 16 selected questions by the HLS-EU. The validity and reliability of the HLS-EU-Q16 in Turkish was conducted by Emiral et al. The scale is a 5-point Likert-type and the answers for each question are scored between 0 and 4. The index score ranges between 0 and 50, and the health literacy level increases as the score obtained from the scale increases [15, 17].

The OSDI is a 12-item scale for the assessment of symptoms related to dry eye disease and their effect on vision. This scale was developed by Walt et al. The validity and reliability of The OSDI in Turkish was conducted by Irkec et al in 2006 [16, 18]. Patients with a score of 13 or above are considered to have dry eye syndrome. The OSDI response structure contains five options that relate to the frequency of the effects of ocular surface disease.

Participants who both previously used or were currently using contact lenses were considered as contact lens users. The family income level was evaluated according to their own perceptions.

Statistical Analysis

The collected data were analyzed using SPSS Statistics for Windows 15.0 (SPSS Inc., Chicago, IL, USA). The normality of the data was analyzed using the Shapiro Wilk test. Chi square, Mann-Whitney U, and Spearman correlation were used for the analyses. $P < 0.05$ was accepted as statistically significant.

3. RESULTS

The study group consisted of 402 (54.8%) male, 331 (45.2%) female patients. The ages of patients ranged between 18-75, with mean (SD) 39.20 (15.0) years. In this study, the percentage of the contact lens users was 28.4% (n=208).

Distribution of study group among contact lens usage and sociodemographic characteristics are given in Table I.

Table I. *Distribution of study group among contact lens usage and sociodemografic characteristics*

Variables	Contact lens usage			Test statistics χ^2; p
	Not use n(%)*	users n(%)*	Total n(%)**	
Age group(year)				
£24	67 (49.2)	69 (50.8)	136 (18.5)	**94.397; 0.001**
25-44	224 (70.5)	119 (29.5)	343 (46.7)	
45-64	171 (94.9)	19 (5.1)	190 (25.9)	
³65	63 (98.4)	1 (1.6)	64 (8.9)	
Gender				
Male	311(77.4)	91(22.6)	402(54.8)	**56.309; 0.001**
Female	214(64.7)	117(35.3)	331(45.2)	
Marital status				
Single	178 (59.5)	121 (40.5)	299 (40.8)	**36.328; 0.001**
Married	347 (80.0)	87 (20.0)	434 (59.2)	
Education level				
Primary school	63 (94.0)	4 (6.0)	67 (9.1)	**55.875; 0.001**
Secondary School	78 (89.7)	9 (10.3)	87 (11.8)	
High school	174 (76.0)	55 (24.0)	229 (40.7)	
University	210 (60.0)	140 (40.0)	350 (47.4)	
Income level				
Good	116(57.4)	86 (42.6)	202(27.5)	**27.750; 0.001**
Moderate	368(76.8)	111 (23.2)	479(65.3)	
Bad	41(78.8)	11(21.2)	52(7.0)	
Chronic eye disease story				
Yes	441(60.1)	203 (39.9)	644(95.4)	**25.816; 0.001**
No	84(94.3)	5(5.7)	89(4.6)	
Total	525(71.6)	208(28.4)	733(100.0)	

**row percantage, ** column percantage*

In this study, the most correctly answered behavior question was "I pay attention to the expiration date of contact lenses" at a rate of 90.9%, while the most incorrectly answered was "I clean contact lenses only when I use them" at a rate of 66.9%. The distribution of the answers to the contact lens-related behavioral questions by the contact lens users is given in the Table II. .

Table II. *Distribution of the answers to the contact lens-related behavioral questions by the contact users*

Contact Lens-Related Behavior Questions	No n (%)	Yes n (%)
1. I pay attention to the expiration date of my contact lenses	19 (9.1)	189 (90.9)
2. I continue to use contact lens solutions after the expiration date*	178 (85.5)	30 (14.5)
3. I clean my contact lenses with tap water*	149 (71.6)	59 (28.4)
4. I clean contact lenses only when I use them*	69 (33.1)	139 (66.9)
5. I always remove my contact lenses before going to sleep	41 (19.7)	167 (80.3)
6. I wash my hands before putting my contact lenses in	32 (15.3)	176 (84.7)
7. I use contact lenses when swimming*	140 (67.3)	68 (32.7)
8. I consult a doctor if there are side effects (flushing, burning, stinging etc.) from contact lens use	56 (26.9)	152 (73.1)
9. I wash my hands before removing my contact lenses	164 (78.8)	44 (21.2)
10. I always consult a doctor when using contact lenses	52 (25.0)	156 (75.0)
11. When I use contact lenses, I go to a doctor for regular check-ups	64 (30.7)	144 (69.3)
12. I remove my lenses before taking a shower	43 (20.6)	165 (79.4)
13. Once a week, I do not wear my contact lens	67 (32.2)	141 (67.8)
14. I have a spare bottle of contact lens solution and lens box	60 (28.8)	148 (71.2)
15. I use the same contact lens storage box until the lens solution runs out*	64 (30.7)	144 (69.3)

** Negative contact lens behaviors*

The scores of the contact lens users obtained from the Contact Lens Behavior Questionnaire ranged from 2-15, with a mean score of 10.6 ± 2.6 (median: 11.0). The distribution of the scores obtained from the Contact Lens Use Behavior Questionnaire according to variables to be related to contact lens usage is given in Table III.

The scores obtained from the OSDI Dry Eye Scale ranged from 0 to 43, the mean score was 14.78±8.7 (median: 14.0). The number of participants with dry eye disease was 429 (58.5%). Contact lens usage was found to have no significant effect on the frequency of dry eye syndrome(X^2=0.503; p=0.478).

The scores obtained from the HLS-EU-Q16 ranged between 0-50 and the mean score was 35.9±10.1 (median: 36.5). The distribution of scores obtained from OSDI Dry Eye Scale and HLS-EU-Q16 are shown in Table IV.

Table III. *The distribution of the scores obtained from the Contact Lens Use Behavior Questionnaire according to variables to be related to contact lens usage*

Variables	n (%)	Median (Min-Max)	Test Statistic z/KW; p
Purpose of contact lens usage			
Correction of refractive errors*	114 (54.8)	11.0 (6.0-15.0)	**9.955; 0.007**
Aesthetic reasons *	79 (38.0)	10.0 (2.0-15.0)	
Other	15 (7.2)	10.0 (5.0-15.0)	
Efficient factor to contact lens usage			
Willingly	125 (60.1)	10 (2.0-15.0)	**23.959; 0.001**
Doctor's advice *	66 (31.7)	11.5 (5.0-15.0)	
Friend recommendation	10 (4.8)	7.5 (4.0-10.0)	
Other	7 (3.4)	9.0 (5.0-12.0)	
Contact lens provided place			
Optical store	120 (57.7)	10.0 (2.0-15.0)	4.332;0.228
Pharmacy	74 (35.6)	11.0 (4.0-15.0)	
Internet	13 (6.3)	13.0 (7.0-13.0)	
Other (beauty saloons etc.)	2 (0.5)	10.5 (10.0-11.0)	
Duration of contact lens use a day			
<8 hour	20 (9.6)	11.0 (8.0-15.0)	2.196;0.334
8-16 hour	172 (82.6)	11.0 (2.0-15.0)	
>16 hour	16 (7.8)	9.5 (6.0-14.0)	
Frequency of sleeping with contact lens			
Always	16 (7.7)	10.0 (5.0-13.0)	7.514;0.057
Often	24 (11.5)	9.0 (8.0-14.0)	
Rarely	103 (49.5)	11.0 (2.0-15.0)	
Never	65 (31.3)	11.0 (5.0-15.0)	
Washing contact lens with water			
Yes	67 (32.2)	10.0 (5.0-15.0)	**2.252;0.024**
No	141 (67.8)	11.0 (2.0-15.0)	
Experience of health problems related to contact lens usage			
Yes	68 (32.7)	10.0 (5.0-15.0)	0.862;0.389
No	140 (67.3)	11.0 (2.0-15.0)	
Level of information about contact lens usage			
Insufficient	17 (8.2)	10.0 (4.0-13.0)	**2.479;0.013**
Sufficient	191 (91.8)	11.0 (2.0-15.0)	
Total	208 (100.0)	11.0 (2.0-15.0)	

** pairwise x2 analysis, p <0.05*

Table IV. *The distribution of scores obtained from OSDI Dry Eye Scale and HLS-EU-Q16*

Contact Lens Usage	n (%)	OSDI Dry Eye Scale	HLS-EU-Q16
		Median (min-max)	Median (min-max)
No	525 (71.6)	15.0 (0.0-43.0)	35.4 (0.0-50.0)
Yes	208 (28.3)	14.0 (0.0-42.0)	**38.5 (8.3-50.0)**
Total	733 (100.0)	14.0 (0.0-43.0)	36.5 (0.0-50.0)
Test Statistic (z; p)		1.394; 0.163	**3.305; 0.001**

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In this study, there was a positive relationship between the scores obtained from the Contact Lens Related Behavior Questions and HLS-EU-Q16 (r=0.159, p=0.022).

The distribution of the scores obtained from the Contact Lens Related Behavior Questions and HLS-EU-Q16 is given in Figure I.

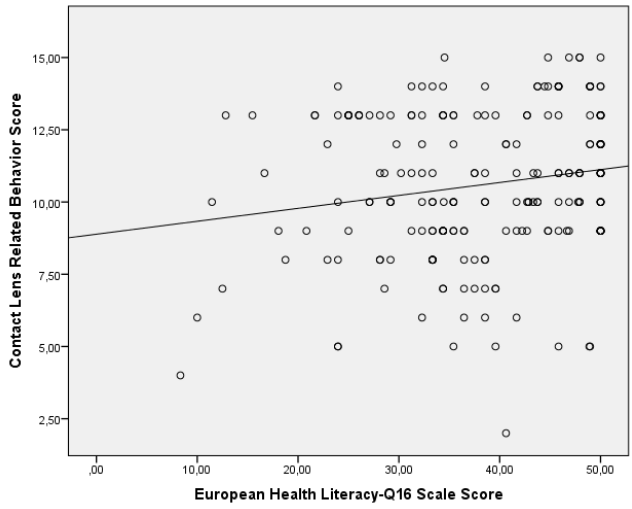

Figure 1. *The distribution of the scores obtained from the Contact Lens Related Behavior Questions and European Health Literacy-Q16 Scale Score*

4. DISCUSSION

This study explored a fairly new field, which evaluated contact lens usage and health literacy among Turkish adults. It was found that there was a positive correlation between health literacy and healthy contact lens usage habits. With this in mind, health literacy is an important factor in proper contact lens usage as well as other healthy lifestyle behaviors.

In the literature review, the percentage of contact lens usage was very wide. In this study, 28.4% of the participants used contact lenses. Generally, studies conducted in developing countries have indicated a high prevalence of contact lens use [10, 19, 20]. A study conducted in Ghana reported that only 3.3% of participants had previously used contact lenses [21]. On the other hand, Aziz et al. and Dinc et al. reported that the percentage of contact lens usage was 38.0% and 34.2% in Malaysia and Turkey, respectively [11, 22]. These different findings may have been the result of differences in the attitudes of the societies towards wearing contact lenses and barriers to accessing contact lens.

Contact lens usage could be affected by many socioeconomical factors. Some studies have reported that gender, age, and economic and educational status are associated with contact lens usage [10, 23]. In the current results, female gender, younger age, and higher economic and educational status were associated with being more likely to use contact lenses. A report from the United States noted that increasing age, male gender, and lower income and educational status were reversely associated with contact lens usage [23]. Ocansey et al., reported that contact lenses were mostly used by younger people [24]. These findings could be related with the use of contact lenses for esthetic and sportive purposes.

Contact lens usage increases the risk of some health problems, such as keratitis and dry eye syndrome. It is already known that extended wear and poor hand hygiene are more important risk factors for contact lens-related microbial keratitis. Failure to properly use contact lenses may be a leading cause of the development of a bacterial biofilm layer. Moreover, extended contact lens usage increases susceptibility to infections due to hypoxic stress [25]. In this study, only 21.2% of the contact lens users washed their hands before handling their contact lenses. Berenson et al., reported that poor hygienic practices were common among contact lens users, and almost half (37%) did not wash their hands before handling their lenses [26]. Furthermore, other recent studies from Germany and the United Kingdom noted that 77.1% and 72.2% of participants always washed their hands before inserting their contact lenses, respectively [27]. The use of proper hygiene behavior among contact lens users, especially hand washing, must be improved.

Another common disease in contact lens wearers is dry eye syndrome. Symptoms of this include sensitivity to light, eye grittiness, and blurred vision [28]. The mechanism of symptoms seems complex. Tear hiperosmolarity and decreased protective effects of the musin layer can cause dry eye symptoms among contact lens users [29]. Contact lens usage was found to have no significant effect on the frequency of dry eye syndrome. A study noted that contact lens users were 5 times more likely than others to report dry eye symptoms [30]. Dry eye syndrome is a symptom-based disease [31]. It can be considered as the cause of different results.

It is known that low health literacy is a problem in the provision of effective health care and has a key role in delaying the uptake of health care [32, 33]. An increase in health literacy will improve health-seeking behaviors, including eye conditions [33]. In this study, the health literacy level of the contact lens users was higher than in the other participants. No studies could be found in the literature that directly addressed or measured health literacy among contact lens users in Turkey. Harrison et al. reported that health literacy is an important factor in gaining more control of an individual's visual health and ophthalmologic diseases could have a negative impact on health literacy [32].

In conclusion, contact lens usage was quite common in the study group. The usage was more frequent in the young and female patients. Only one in five patients reported that they washed their hands before removing their contact lenses. The health literacy level was higher in the contact lens wearers. A positive correlation was found between the scores of the health literacy scale and the answers to the contact lens-related behavior questions. Ophthalmologic diseases could have a negative impact on health literacy. Further studies on contact lens use and health literacy are needed.

Compliance with Ethical Standards

Ethical Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Eskisehir Osmangazi University. Informed consent was obtained from all patients prior to examination.

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Author Contibutions: GD: Study planning, Data collection and processing, Analysis and interpretation of data, writing the report, AU: Study planning, Analysis and interpretation of data, writing the report, SP, EEO and DA: Study planning, Data collection and processing, writing the report, TS: Study planning, writing the report. All authors read and approved the final version of the article.

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Does re-amputation following lower extremity amputation in diabetic or dysvascular patients negatively affect survival?

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ABSTRACT

Objective: We aimed to investigate the characteristics of patients who underwent unilateral amputation due to diabetes and peripheral artery disease, as well as the risk factors that cause re-amputation, and to determine these patients' survival status and the risk factors for mortality.

Patients and Methods: This retrospective study included 133 patients who underwent amputation due to diabetes and peripheral arterial disease between 2012 and 2018. The etiology of amputation, the re-operation rate and time to re-operation following initial amputation, survival status and follow up results were accessed from hospital records.

Results: Twenty-eight patients underwent amputation due to peripheral arterial disease, whereas 105 patients had peripheral vasculopathy due to diabetes mellitus. The re-operation rate was 33.8%, and the median period from initial surgery to the second surgery was six-weeks. Sixty-six deceased patients survived with a median of 6 months following initial operation.

Conclusion: The most crucial factor causing re-amputation was the non-healing wound problems. Patients with amputation should be followed up carefully for wound problems in the six weeks after surgery. Advanced age, American Society of Anesthesiologist grade 4 patients, associating neurological disease, low albumin level, low lymphocyte count and postoperative intensive care unit requirement were all poor prognostic factors for survival. Re-amputation had no negative effect on survival.

Keywords: Amputation, Diabetes mellitus, Lower extremity, Reoperation rate, Mortality, Peripheral arterial disease

1. INTRODUCTION

Wound problems on extremities may occur due to the complications of diabetes mellitus (DM) or peripheral artery disease (PAD). If wound problems are not treated appropriately in time, the infection can spread to deeper tissues of the entire lower extremity, and irreversible damage may develop in the extremity [1]. Conventional dressing, negative pressure wound therapy, debridement, and amputation can be applied for these wound problems depending on the wound's depth and the severity of the infection [2,3].

Patients diagnosed with DM or PAD should be informed about the prevention of foot wound problems. They should be followed up for foot examination at least once a year [4].Diabetic patients have a up to 25% risk of developing foot ulcers in whole life [5].Healing ulcers recur 40% within one year and 65% within five years [6]. PAD and DM are commonly associated with vasculopathy related amputations and are eight times more common than traumatic amputations [7].

We aimed to investigate the characteristics of patients who underwent unilateral amputation due to DM or PAD, as well as the risk factors that cause re-amputation in our institution and also to determine these patients' survival status and the risk factors that cause mortality.

2. PATIENTS and METHODS

This study was conducted upon the approval of Marmara University, School of Medicine Ethics Committee (09.2021.16). A retrospective review was done using the medical records of 262 patients who underwent amputation between 2012 and 2018. Patients with bilateral amputation (n=27) and without regular follow-up (n=13) were excluded from the study. The patients who underwent amputation due to malignant extremity tumors (n=57) and trauma and trauma related complications (n=32) were also excluded. The remaining 133 patients who

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underwent unilateral lower extremity amputation due to DM or PAD were included in this study.

Demographic characteristics of the patients (age, gender), comorbidities, nutritional status (albumin level), blood parameters [Complete blood count (CBC), hemoglobin (Hb) (g/dl), glycated hemoglobin (HbA1c) (%), C-reactive protein(CRP) (mg/dl)], the American Society of Anesthesiologists (ASA) grades, microbiological culture positivity, the etiology of amputation, need for reoperation, amputation level in the first operation, type of surgery (debridement, revision of the amputation to a higher level) performed for patients requiring a reoperation, postoperative intensive care unit (ICU) requirement after the first operation, the length of ICU stay, the length of hospital stay in the first operation, the time from the first operation to reoperation, the survival status of the patients, duration of follow-up were recorded from the patients' archive files.

The lower extremity amputation level of the patients was determined by preoperative Doppler ultrasonography or computed tomography angiography, and intraoperative observation of the tissue viability.

Statistical Analysis

Data analysis was carried out using SPSS, v. 22.0 software (SPSS Inc., Chicago, Illinois, USA). The study data were evaluated using descriptive statistical methods (mean, standard deviation, median, interquartile range, frequency, ratio, minimum, maximum). A Kolmogorov-Smirnov test, a Shapiro-Wilk test, and graphical assessments were used to test the normality of the quantitative data distribution. The Mann-Whitney U test was used to compare continuous variables that were not distributed normally. Categorical variables were compared with Chi-squared test, Fisher's Exact test, and Fisher-Freeman-Halton tests. A Kaplan Meier Survival analysis and Log-Rank test were used to evaluate the survival data. A p-value less than 0.05 was considered statistically significant.

3. RESULTS

The study included 133 patients who underwent amputation of the lower extremity at our clinic between 2012 and 2018 with a diagnosis of DM or PAD.

Characteristics of patients according to amputation etiology are shown in Table I.

Table I. *Characteristics of the patients by amputation etiology*

Characteristics	Diabetes Mellitus	PAD	p
Age (years) (Mean±Sd)	63.67±9.97	69.29±16.01	0.019a
Sex			
Men	88 (83.8%)	20 (71.4%)	0.136b
Women	17 (16.2%)	8 (28.6%)	
The Need of Second Operation	37 (35.2%)	8 (28.6%)	0.508b
Time from First Operation to Second Operation (month)*	1.35 (0.67-3.5)	1.75 (0.78-2.88)	0.823a
Culture			
Positivity	53 (50.5%)	11 (39.3%)	0.526c
Negative	8 (7.6%)	3 (10.7%)	
NA	44 (41.9%)	14 (50%)	
Comorbidities (0/1/2/3/4)	0/28/36/28/13	7/13/3/5/0	<0.001c
CAD	48 (45.7%)	8 (28.6%)	0.103a
CRD	35 (33.3%)	2 (7.1%)	0.006a
Neurologic	13 (12.4%)	5 (17.9%)	0.534d
COPD	8 (7.6%)	4 (14.3%)	0.277d
ASA grade			
2	18	5	0.754c
3	67	16	
4	20	7	
Postoperative ICU requirement	40 (38.1%)	11 (39.3%)	0.908b
Length of Stay in ICU (day)*	2 (1-5)	2 (1-4)	0.857a
Length of Stay in hospital (day)*	13 (5-26.5)	7.5 (5-21.5)	0.346a
Survival Status			
Surviving	56 (53.3%)	11 (39.3%)	0.187b
Deceased	49 (46.7%)	17 (60.7%)	
Follow-up (month)*	19 (6.5-39.5)	17.35 (4.15-49.25)	0.842a

[a] *Mann Whitney U Test, b Pearson Chi-Square Test, c Fisher Freeman Halton Test, d Fisher Exact Test*

PAD: Peripheral Arterial Disease, CAD:Coronary Arterial Disease, CRD:Chronic Renal Disease, COPD; Chronic Obstructive Pulmonary Disease, ICU: Intensive Care Unit, ASA: American Society of Anesthesiologists

**: These data are presented as median IQR. Other data are number of patients.*

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The distribution of amputation level in the first operation and type of surgery (debridement, revision of the amputation to a higher level) for re-operation of the patients are presented in Table II. The re-operation rates of patients who underwent above the knee amputations were significantly lower than those below the knee level amputations (p<0.001).

Table II. *Characteristics of amputation level in the first operation, type of surgery (debridement, revision of the amputation, a higher level amputation). for.re-operation.*

First Operation	n (%)	Re-operation	n (%)	First Operation to Re-Operation	n (%)
Finger amputation	15 (11.2%)	Debridement	15 (11.3%)	Finger amputation to debridement	1 (2.2%)
TMA	28 (21.1%)	TMA	1 (0.8%)	Finger amputation to TMA	1 (2.2%)
BKA	58 (43.6%)	BKA	11 (8.3%)	Finger amputation to BKA	4 (8.9%)
AKA	32 (24.1 %)	AKA	16 (12%)	Finger amputation to AKA	1 (2.2 %)
		HLFA	1 (0.8%)	TMA to debridement	3 (6.7 %)
		Hip Disarticulation	1 (0.8%)	TMA to BKA	7 (15.6%)
				TMA to AKA	2 (4.4%)
				BKA to debridement	8 (17.8%)
				BKA to AKA	13 (28.9)
				AKA to debridement	3 (6.7%)
				AKA To HLFA	1 (2.2%)
				AKA to Hip disarticulation	4 (8.9%)

TMA: Trans-metatarsal amputation, BKA: Below the knee amputation, AKA:Above the knee amputation, HLFA: High Level Femoral Amputation

Table III. *Assessments related to mortality in all cases*

Characteristics	Surviving	Deceased	p
Age (years) (Mean±Sd)	61.21±11.52	68.55±10.69	<0.001a
Sex			0.792b
Men	55 (82.1%)	53 (80.3%)	
Women	12 (17.9%)	13 (19.7%)	
The Need of Second Operation	20 (29.9%)	25 (37.9%)	0.328b
Time from First Operation to Second Operation*	1 (0.67-3)	1.5 (0.85-3.5)	0.475a
Culture			0.612b
Positivity	34 (50.7%)	30 (45.5%)	
Negative	4 (6%)	7 (10.6%)	
NA	29 (43.3%)	29 (43.9%)	
Comorbidities (0/1/2/3/4)	2/22/24/14/5	5/19/15/19/8	0.296c
CAD	25 (37.3%)	31 (47%)	0.259b
CRD	15 (22.4%)	22 (33.3%)	0.312b
Neurologic	5 (7.5%)	13 (19.7%)	0.039b
COPD	6 (9%)	6 (9.1%)	0.978b
Postoperative ICU requirement	20 (29.9%)	31 (47%)	0.042b
Length of Stay in ICU (day)*	0 (0-1)	0 (0-2)	0.034a
Length of Stay in hospital (day)*	10 (5-21)	13 (5-27)	0.139a
ASA grade			0.038b
2	16 (23.9%)	7 (10.6%)	
3	42 (62.7%)	41 (62.1%)	
4	9 (13.4%)	18 (27.3%)	
Follow-up (month)*	32 (16-60)	6.5 (1-29)	<0.001a

a Mann Whitney U Test, b Pearson Chi-Square Test, c Fisher Freeman Halton Test
*CAD: Coronary Arterial Disease, CRD:Chronic Renal Disease, COPD: Chronic Obstructive Pulmonary Disease, ICU: Intensive Care Unit, ASA: American Society of Anesthesiologists. *: These data are presented as median IQR. Other data are number of patients.*

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Regarding the analyses of the blood parameters of the patients in the preoperative period, the median interquertile range (IQR) values of hemoglobin (g/dl), hematocrit (%), white blood cell (x10^3/µl), neutrophil (x10^3/µl), lymphocyte (x10^3/µl), platelet (x10^3/µl), albumin, and CRP (mg/L) were 10 (9-11), 30 (27.5-34), 10 (8-14), 8 (6-12), 1 (1-2), 314 (241-402), 3 (2-3), and 92.5 (38.75-149.5), respectively. Blood parameters were similar between patients with amputation due to DM and PAD. The median (IQR) value of HbA1c (%) in diabetic patients was 7.65 (6.73-9.28). Thirty (22.6%) patients with albumin values above 3.5g/dL, 14 (10.5%) patients with Hb values above 12g/dL and 49 (36.8%) patients with lymphocyte count above 1.5 x10^3/µl were detected.

Among the 75 (56.4%) patients who had wound culture test, culture positivity was detected in 64 (85%). The single microorganism [S. Aureus (n = 11), P. Aeruginosa (n = 8), E. Coli (n = 5), E. faecium (n = 3), others (n = 7)], was detected in 34 patients (53.1%) and polymicrobial microorganism (mostly gram-negative and anaerobic microorganisms) in 30 patients (46.9%). It was determined that more wound culture tests were examined in the patients who needed a re-operation than those with a single surgery (p<0.001).

No statistically significant risk factors were found regarding the characteristics of recovery between patients who underwent a single surgery and those requiring re-operation (p>0.05). When these two groups were compared in terms of survival, there was no statistically significant difference (p=0.439).

Table III presents the assessments related to mortality in all cases. There were statistically significant differences between the blood parameters of the surviving and deceased patients, with lymphocyte count (p=0.044) and albumin level (p=0.018) being significantly lower in the deceased patients. Although, it was remarkable that a high CRP level had a higher mortality rate, this relationship was not statistically significant (p = 0.056).

Among the 105 patients who underwent amputation due to DM, 56 (53.3%) patients survived with a median survival time of 60±13.55 months. 11 (39.3%) of the 28 cases had an amputation due to PAD survived with a median survival time of 29±11.98 months. When assessing survival status between the groups using a Log-Rank test, no statistically significant difference was noted between the two groups' survival curves (p=0.298) (Figure 1). Sixty-six deceased patients survived with a median (IQR) value of 6 (1-29) months following the initial operation.

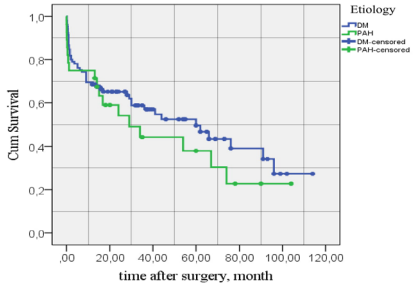

Figure 1. *Kaplan Meier Analysis of patients undergoing amputation due to diabetes mellitus and peripheral arterial disease*

4. DISCUSSION

We evaluated 262 patients who underwent extremity amputation in our clinic between 2012 and 2018 with various indications; 50.7% were due to DM or PAD. 80% of these patients were male, and the median age was 65 years. This rate was similar to reported amputation rates due to DM or PAD in the literature [8, 9].

There are no clearly defined criteria for determining the amputation level of a patient for whom an amputation decision is made due to DM or PAD [10]. Although, various invasive and non-invasive vascular methods have been reported in the literature for selecting the appropriate level of amputation [11], we think that the most crucial criterion for selecting amputation level is to evaluate both preoperative vascular imagines and observe the bleeding of tissues intraoperatively. Performing amputation at the distal level as much as possible aims to reduce the patient's energy during walking and improves the quality of life [12,13]. However, distal level amputation may cause wound problems and risk of re-operation [13]. The re-operation risk ratio was reported as 13.4-56% (average 16.3%) in the literature [14]. In our study, the re-operation rate was 33.8%, which was above the average re-operation rate reported in the literature. This high rate may have been due to our goal to preserve the most distal level as possible and to improve the patient's quality of life and facilitate mobilization. Also, amputation surgery is a form of treatment that is accepted very difficult in certain societies. It is reported that the psychosocial structure of patients is impaired after amputation surgery [15]. In our clinical practice, we also observed that patients' self-care after surgery had decreased significantly which might cause the need for a secondary surgery. On the other hand, as we found that re-operation did not affect the mortality rate, we considered this re-operation rates as reasonable. Patients who should undergo amputation at the possible distal level to avoid the impairment of their quality of life and functionality.

Many factors affect wound healing in patients after amputation surgery [14, 16-19]. The median period from the initial surgery to the second surgery was six weeks in our study. 2-2590 days were reported in the literature from the first operation to reoperation [17]. The general opinion is that these patients should be closely followed-up within the first six months [20].Although, various risk factors for reoperation (coronary artery disease, chronic kidney failure, low albumin levels, low lymphocyte count, anemia) were reported [13,16,17,21,22], we did not find a statistically significant relationship between the risk factors and re-operation in this study. This may be explained by the fact that the majority of our patients have already these risk factors. Also, it reveals the importance of performing the amputation operation at the appropriate level.

Mostly, gram-negative and anaerobic bacteria are responsible for serious deep wound infections and life-threatening conditions [23]. The microorganisms isolated from wound cultures of patients were primarily gram-negative bacteria in the current study. This situation may be explained by the chronicity of the diabetic wounds and previous antibiotic treatments. We

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did not perform any wound culture in patients who received preoperative antibiotic treatment. Culture positivity was detected in 64 (85.3%) out of 75 patients.

When we examined the survival status of patients who underwent amputation due to DM or PAD, we found that 66 (49.6%) of the patients died within a median of 6 months after the inital surgery. Comorbidity, older age and gram-negative microorganisms have been reported to be the factors that negatively affect the patients' survival [23, 24]. The rate of comorbid disease was significantly higher in diabetic patients. The mean age of patients with PAD was statistically significantly higher than diabetic patients. The high mortality rate in patients amputated due to DM or PAD may be attributed to comorbid status of these patients and their advanced age.

The limitations of the present study include its single-center and retrospective study design, the lack of a control group, the small number of patients, the lack of cost analysis, and the operations were performed by different surgeons at our department.

In conclusion, the most critical factor for wound healing after amputation surgery, regardless of the risk factors reported in the literature, was amputation level. Patients with amputation should be followed up carefully for wound problems in the first six weeks after surgery. Older age, ASA-4 patients, with neurological disease, low albumin level, low lymphocyte count and postoperative ICU requirement were all poor prognosis criteria in terms of survival. Re-amputation surgery had no negative effect on survival.

Compliance with the Ethical Standards

Ethical Approval: Marmara University, School of Medicine Ethics Committee approved the study (protocol no: 09.2021.16).

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Conflict of Interest: The authors have no potential conflicts of interest to disclose.

Author Contributions: OB: Study design, data analysis, writing the article, WJM and BG: Data collection, data analysis, BE: Study design, writing the article, supervision. All authors read the article and approved the final version of the article.

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Role of diffusion-weighted imaging and dynamic contrast enhanced magnetic resonance imaging in the diagnosis of early sacroiliitis in seronegative spondyloarthropathies, correlation with levels of acute phase reactants

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ABSTRACT

Objective: Seronegative spondyloarthropathy (SpA) is a destructive disease. Early diagnosis is crucial to prevent morbidity. Magnetic resonance imaging (MRI) is the only imaging modality that can show early sacroiliitis. We aimed to investigate the utility of dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) and diffusion-weighted imaging (DWI) in the detection, quantification and staging of early/acute SpA. We also investigated the relationship between contrast enhancement properties and apparent diffusion coefficient (ADC) values with laboratory parameters for inflammation such as ESR and CRP measurments.

Patients and Methods: Dynamic contrast-enhanced magnetic resonance imaging and DWI were performed on 85 patients that fulfilled the criteria. A positive MRI finding was defined as inflammation in subchondral bone representing active sacroiliitis. Kinetic analyses were performed, apparent diffusion coefficient (ADC) values were calculated, ESR and CRP levels were measured for quantification of inflammation. Statistical analyses were performed.

Results: In acute SpA group; quantity, area and level of enhancement, values of ADC and Fenh, levels of CRP were significantly higher than those with chronic SpA. A high level of agreement was found between the ADC threshold value of $0.831x10^{-3}$ mm2/s and diagnosis according to Assessment of SpondyloArthritis International Society (ASAS) criteria (Kappa=0.794;p<0.001).

Conclusion: Dynamic contrast-enhanced magnetic resonance imaging and DWI are advanced MR techniques which enable quantification of active inflammation. They are hallmarks for early SpA. Their combined use is superior to one alone in the diagnosis of early sacroiliitis.

Keywords: Seronegative spondyloarthropathy, Early sacroiliitis, Dynamic contrast enhanced magnetic resonance imaging, Diffusion-weighted magnetic resonance imaging, Acute phase reactants

1. INTRODUCTION

Seronegative spondyloarthropathy (SpA) is a heterogeneous group of rheumatic disease with unknown aetiology [1]. The spectrum comprises three clinical components as axial SpA, peripheral SpA, and extra-articular manifestations [2]. The diagnosis of axial SpA is mainly based on clinical manifestations related to imaging findings and laboratory data [3].

Seronegative spondyloarthropathy is a disabling disease that directly affects the quality of life, so early diagnosis is a crucial step due to new treatment options that can be available, to regress the inflammation and delay disease progression [4,5].

The Assessment of SpondyloArthritis International Society (ASAS) criteria for classification of axial spondyloarthritis introduced active sacroiliitis as one of the most important factors in the classification of SpA [3]. Magnetic resonace imaging (MRI) of the sacroiliac joints (SIJs) plays a key role in early diagnosis because active inflammatory lesions of sacroiliitis can be visible long before structural changes are detectable on radiograpy or computed tomography (CT). Thus, in 2009, ASAS published new criteria for SpA and added an magnetic resonance imaging (MRI) definition to enable the identification of patients without evidence of structural change

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on radiography. The major MRI finding of active sacroiliitis is osteitis (O) or bone marrow oedema (BMO) owing to its importance in the early diagnosis of SpA. Other signs of inflammation, such as enthesitis, capsulitis, and synovitis, can also be observed on MRI [3,6].

Dynamic contrast enhanced magnetic resonance imaging, allows quantification of inflammation by measuring the distribution profile of paramagnetic contrast medium in microvessels and interstitial spaces of the tissues investigated [7]. Synovitis/capsulitis as an indicator of active inflammation can only be shown after contrast administration, so DCE-MRI provides significant additive information to evaluate inflammation.

Diffusion-weighted imaging is an MR based technique that produces image contrast by the different randomized motions of water protons in various biological tissues. Numerous studies have been reported that DWI is a useful tool for detecting inflammatory lesions and quantitative monitoring of inflammatory activity in patients with SpA [8,9].

Management of SpA is based on assessment of disease activity determined by clinical signs and symptoms and levels of acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in addition to structural changes. These are established measures of disease activity to increase sensitivity for diagnosing and monitoring the disease [10,11].

The purpose of this study was to determine the role of DCE-MRI and DWI in the diagnosis of acute (early) sacroiliitis in patients with axial SpA. We also investigated the relationship between contrast enhancement properties and apparent diffusion coefficient (ADC) values with laboratory parameters for inflammation such as ESR and CRP measurements.

2. PATIENTS and METHODS

This study was conducted according to Good Clinical Practice guidelines and was approved by the Haydarpasa Numune Training and Research Hospital Ethics Committee (17.03.2014, 2014/18). Informed consent was obtained from all patients prior to examination.

Patient Selection

The study population comprised 98 patients who were referred by the clinicians from the departments of Physical Medicine and Rehabilitation, Internal Medicine and Gastroenterology, between March 2014 and September 2017. The patients were evaluated with the guidance of ASAS. All of them underwent DCE-MRI. 85 patients that fulfilled the diagnostic criteria for SpA were enrolled in the study.

Thirteen patients were excluded because of not meeting the ASAS criteria, received other diagnoses such as osteoarthritis, with a history of injury or malignancy, and insufficient quality of the images.

MRI acquisition

All the patients were examined on a 1.5 T MRI scanner (GE Optima MR450w) using a 6-channel body coil, in the supine position and the knees flexed 15°. The acquisition was planned in paraaxial images which were parallel to the long axis of the upper part of the sacrum (at an angle of approximately 30-45° to the body axis) and coronal oblique images which were perpendicular to the paraaxial plane, after the sagittal scout image was taken.

Imaging protocol was performed as follows; Coronal Oblique and Axial T1W sequences (TR/TE: 680/42 ms, matrix: 256 × 256, NEX: 2, Slice Thickness: 3 mm, flip angle 90 and FOV: 20-25 cm),Coronal Oblique T2* GRE sequence (TR/TE: 613/7 ms, matrix: 256 × 256, NEX: 2, Slice Thickness: 3 mm, flip angle 90, FOV: 20-25 cm),Coronal Oblique Short Tau Inversion Recovery (STIR) sequence (TR/TE: 4000/85 ms, matrix: 256 × 256, NEX: 2, Slice Thickness: 3 mm, flip angle 90, FOV: 20-25 cm),Coronal Oblique DWI sequence(single-shot spin-echo echo-planar imaging (EPI), b=400/b=800 mm2/s, TR/TE:5200/70 ms, matrix 192 × 192, NEX: 2, Slice Thickness: 3 mm, flip angle 90, FOV: 20-25 cm),Coronal precontrast and postcontrast dynamic fat sat T1W sequence; (TR/TE:400/20 ms, matrix: 256 × 256, NEX: 2, Slice Thickness: 3 mm; flip angle 10 and FOV: 20-25 cm). Dynamic imaging was performed after injecting Gadoterate Meglumine (Dotarem®, Guerbet, France) in the antecubital vein at 0.1 mmol/kg, the flow rate at 3 ml/sec. Consecutive 1st, 2nd, 3rd and 4th minute images were obtained (Figures 1a-f and Figures *2a-g).*

The DWI original data were analyzed using GE workstation 3.0. ADC maps were obtained. 80-100 mm^2 circular ROI's were placed on the hypointens lesions, an average value of ADC was calculated. The ROI selection was performed by avoiding the joint space, bone cortex, bone sclerosis area, blood vessels, and artifacts.

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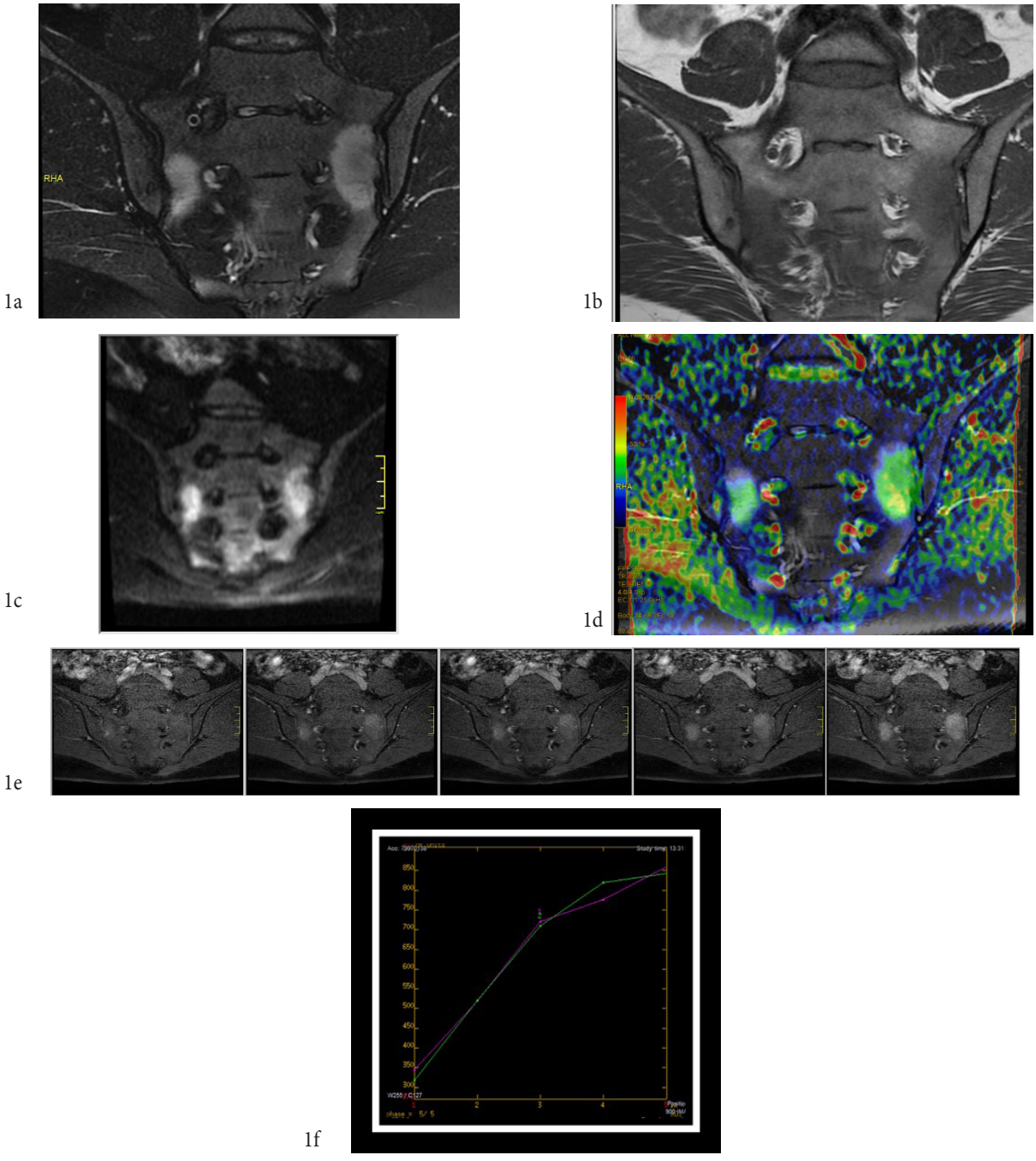

Figure 1(a-f). *MRI of SIJ's in semicoronal planes in a 26-year-old male with inflammatory low back pain of 4 months duration. CRP was 42.3 mg/L . (a) STIR sequence shows abnormal increased signal in sacrum bilaterally, typical for BMO/O due to acute inflammatory sacroiliitis. Lesions are periarticular-subchondral in location, of significant size. (b) There are corresponding areas of diminished signal intensity on the T1W sequence. (c,d) Affected regions show restricted diffusion with high signal intensity on DWI. (e) On dynamic contrast enhanced series, lesions show progressive enhancement rising with time. (f) On the kinetic analysis, a Type 3 TSI curve is obtained with a rapid initial upslope followed by a persistent rise*

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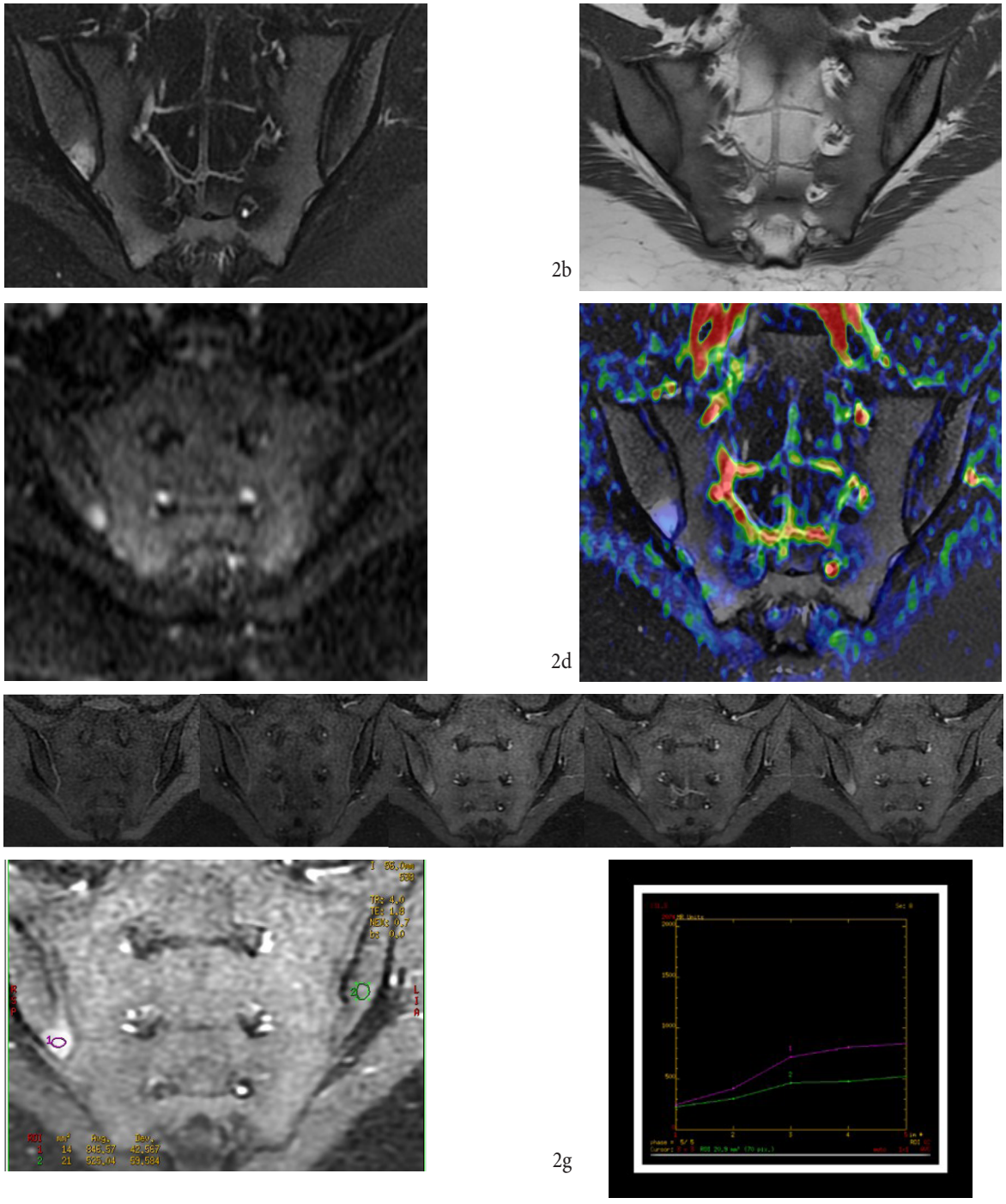

Figure 2(a-g). *A 32-year-old male with inflammatory low back pain of more than 1 year duration. CRP was 21.2 mg/L. (a) STIR sequence shows a subchondral high signal area at the iliac side of the right SIJ pointing to acute inflammation. (b) There is a corresponding focus of low signal intensity on the T1W sequence. Additionally, bilateral periarticular subchondral sclerosis is present on iliac and sacral aspects of SIJ's as hypointensities on STIR and T1W sequences consistent with chronic. (c,d) The lesion shows restricted diffusion on DWI. (e) On dynamic contrast enhanced series, the lesion shows delayed enhancement rising with time compared with the contralateral iliac bone. (f,g) On the kinetic analysis, a Type 2 TSI curve is obtained with a slow initial upslope followed by a continued slow rise*

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Image analysis

Images were analysed by a radiologist with 5 years of experience in musculoskeletal imaging, blinded to clinical and laboratory data, at GE workstation 3.0.

Active lesions in sacroiliitis were defined as;

1. Bone Marrow Oedema; subchondral increased signal intensity in the bone marrow on short tau inversion recovery (STIR) or fat-saturated T2W (FS-T2W) sequence, in typical anatomical areas for SpA inflammation (Figure 1a and Figure 2a), 2. Enthesitis; increased signal in the bone marrow and/or soft tissue on STIR and/or fat-saturated T1W (FS-T1W) postcontrast images at sites where ligaments and tendons attach to the bone, 3. Capsulitis; increased signal on STIR and/or FS-T1W postgadolinium images at sites where synovia is present, 4. Synovitis; Gadolinium-enhanced synovium and increased synovial volume detected by MRI.

Structural lesions in sacroiliitis were defined as;

1. Erosion; a defect in the subchondral bone with loss of the dark signal of the subchondral bone plate, 2. Fat Metaplasia; subchondral increased signal intensity reprehensive of fat in the bone marrow on T1 and decreased signal on STIR or FS-T2W sequences, 3. Backfill; the presence of high T1 signal intensity within an erosion at the joint surface, 4. Ankylosis; bony bridges or confluent high T1 signal intensity bridging across the joint space to connect between the ilium and sacrum, 5. Sclerosis; area with very low signal intensity on all sequences located in the subchondral bone with a depth of at least 5 mm.

According to ASAS, a 'positive MRI' was defined as the observation of inflammation in the subchondral bone representing active sacroiliitis. Without the presence of BMO/O; neither other findings of active inflammation nor structural lesions reflecting old inflammation are sufficient for diagnosis [3].

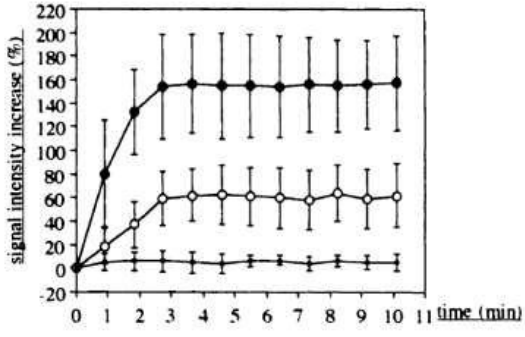

Figure 3. *Time-signal intensity (TSI) curves. The kinetic analysis revealed three types of curves that showed either a plateau (Type 1 curve), or an increase with slow initial upslope (Type 2 curve) or rapid initial upslope (Type 3 curve).*

On DCE-MRI, in the presence of contrast enhancement, a time-signal intensity (TSI) curve was obtained by placing an 80-100 mm^2 circular region of interest (ROI) in maximum enhanced area of the articular cartilage, synovium, joint capsule, and subchondral bone marrow (Figure 2f). The kinetic analysis took four minutes of repetitive scanning in total and led to three types of the curve which showed either a plateau, or an increase with slow initial upslope or rapid initial upslope (Figure 3). The initial signal intensity (SI_0) and the maximum signal intensity (SI_{max}) were automatically exhibited on the curve. Additionally, the semiquantitative index enhancement factor (F_{enh}) was calculated from the time-signal intensity curve by using OriginPro software (Origin Lab, Northampton, MA, USA). The following mathematical formula was used for the measured data and expressed as %.

$$F_{enh} = \frac{SImax - SI0}{SI0} x100$$

Depending on data derived from DCE-MRI cases were classified as:

1. $F_{enh <}$ 20% and TSI curve upslope < 10% (Type 1 curve); no sacroiliac inflammation,

2. F_{enh} >20% and TSI curve upslope > 10% (Type 2 curve); mild sacroiliac inflammation,

3. F_{enh} >90% and TSI curve upslope > 40% (Type 3 curve); severe sacroiliac inflammation.

In the presence of active sacroiliitis, the activity index was categorized as > follows**:** $F_{enh} \leq$ 25% (Grade X), F_{enh} 25%-70% (Grade A), F_{enh} 70% (Grade B).

On DWI, selected ROI's were placed on the obvious lesions in the image whose location and the area were consistent with the previous images. Average value of ADC was calculated and recorded as $x10^{-3}$ $mm2/s$.

As acute-phase reactants, CRP and ESR are established measures of disease activity. Blood tests were performed 2 to 5 days before MR imaging. ESR≥20 mm/hr and/or CRP≥0.5 mg/L values were considered high.

Statistical Analysis

IBM SPSS Statistics, Version 23.0 (SPSS Inc., Chicago, USA) and MedCalc® Statistical Software Version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) analysis programmes were used in this study. Descriptive statistics for both groups were reported as frequency and percentages within the groups (n, %). Before analyzing the relationship of continuous numerical variables between groups, normality testes were performed considering the number of samples in the groups, such as Kolmogorov-Smirnov and Shapiro-Wilk tests, and histogram graphics. Accordingly, normally distributed variables were reported as mean±standard deviation, and non-normally distributed variables were reported as median (min-max). Student's t-test, in which the mean values were compared for those with normal distribution, and the Mann-Whitney U test, where the median values were compared for those who did not show normal distribution, were used to analyze the difference between the two groups in terms of numerical variables. The

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difference in the distribution of categorical data between the groups was evaluated with the Chi-square test. Relationships between parameters were evaluated with Pearson or Spearman correlation tests and Kappa concordance analyses. ROC curve analyses were implemented to evaluate the performance of the parameters in the diagnosis of acute sacroiliitis and to determine the appropriate threshold values. Accordingly, AUC, sensitivity and specificity values were reported. P values less than 0.05 were considered significant.

3. RESULTS

Among 85 patients who were diagnosed as SpA based on clinical and imaging findings, 36% (n=31) were identified as acute SpA, while 64% (n=54) were in the chronic SpA group.

In acute SpA group; 13 (41.9%) of 31were female and 18 (58.1%) were male. The median age was 32 (18-45) years. There was no statistical difference in terms of gender between acute and chronic SpA patients (p=0.123). However, patients with chronic SpA were significantly older (p=0.033).

Involvement of the SIJs, was unilateral in 11 out of 31 (35.5%) acute cases, and bilateral in 20 (64.5%). Of those with unilateral involvement, 5 (45.5%) had right joint inflammation, and 6 (54.5%) had left joint inflammation.

The median CRP level in patients with active sacroiliitis was 0.56 mg/dL (0.01 mg/dL – 4.49 mg/dL) and the median ESR level was 19 mm/hr (1 mm/hr – 78 mm/hr). CRP values of patients with acute SpA were significantly higher than those with chronic SpA (p=0.037). There was no statistical difference between the two groups in ESR values (p=0.154).

The mean and the median ADC measurements of the acute SpA cases were 1.05 ± 0.57 $x10^{-3}$ mm/s and 0.84 (0.4-2.61 $x10^{-3}$ mm2/s), respectively. They were significantly higher than the patients with chronic SpA (p<0.001 and p=0.027). Demographic characteristics, laboratory findings and mean ADC values of the patients are summarized in Table I.

On DCE-MRI, SIJs were contrast enhanced in 27 (87.1%) cases with acute SpA, but there was only1 case (1.8%) among patients with chronic SpA. Enhancement was significantly higher in patients with acute SpA than those with chronic SpA (p<0.001). The rate of being acute was considerably higher in cases with contrast enhancement than those without contrast enhancement (p<0.001). TSI curves in the acute group were as follows with decreasing frequency; Type 2 curve in 15 cases (48.3%), Type 3 curve in 13 (41.9%), and Type 1 curve in 13 (41.9%). Type 2 and Type 3 curves were not obtained in any of the chronic SpA patients. The activity index was detected as grade B with the highest frequency (64.5%). Furthermore, in the group showing contrast enhancement, ADC values were significantly higher than those who lacked enhancement (p<0.001), likewise CRP and ESR measurements (p=0.032 and p=0.037, respectively).

Table I. *Demographic, laboratory, and imaging characteristics of the acute SpA and chronic SpA groups*

Characteristics		Acute SpA	Chronic SpA	p value
Gender, n(%)	Male	18 (58.1)	22 (40.7)	0.123
	Female	13 (41.9)	32 (59.3)	
Age (years), median (min-max)		32 (18 – 45)	36 (21 – 61)	0.033
Contrast enhancement, n(%)	(-)	4 (12.9)	53 (98.1)	<0.001
	(+)	27 (87.1)	1 (1.9)	
CRP (mg/L), median (min-max)		0.56 (0.01 – 4.49)	0.2 (0.01 – 4.7)	0.037
ESR (mm/hr), n(%)		19 (1 – 78)	14 (3 – 68)	0.154
ADC ($x10^{-3}$ mm2/s)	mean±SD	1.05 ± 0.57	0.57 ± 0.12	<0.001
	median (min-max)	0.84 (0.4 – 2.61)	0.612 (0.3 – 2.07)	0.027

The diagnostic performance of ADC values for acute SpA was evaluated using ROC curve analysis. It was revealed a sensitivity of 83.9% and a specificity of 94.4% for cut-off value of >0.831x10 $^{-3}$ mm2/s (AUC: 0.903; p<0.001) (Figure 4). Furthermore, a high level of agreement was found between this ADC threshold value and diagnosis according to ASAS criteria (Kappa=0.794; p<0.001).

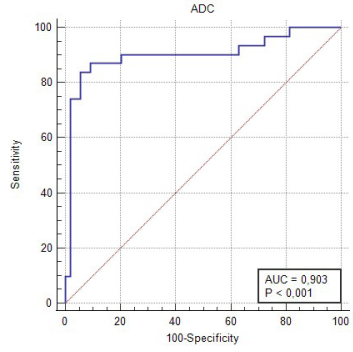

Figure 4. *ROC curve analysis for the diagnostic performance of ADC values*

Consequently, 28 among 31 (90.3%) cases with acute SpA were diagnosed on MRI. While 27 (87.1%) of them were detected by DCE-MRI, 26 (83.9%) cases were diagnosed by DWI features.

4. DISCUSSION

Early diagnosis of sacroiliitis allows reducing morbidity by suggesting an effective treatment plan and appropriate follow-up protocol in patients with SpA [12].

Clinical evaluation has a limited place in the acute SpA diagnosis. Definitive diagnosis is usually achieved via radiological evaluations [13]. Conventional radiography (X-ray) of SIJs is the traditional method for detecting sacroiliitis and diagnosing SpA, but it has limitations such as high interreader variability, the use of ionizing radiation, delay in diagnosis of 8–11 years,

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since it takes time to develop structural damage visible on radiographs. It is difficult to diagnose sacroiliac inflammation with conventional radiography in early and acute phases since its diagnostic capacity is limited in the period when chronic changes have not yet occurred. In contrast, MRI of SIJs can visualize both inflammatory lesions and structural damage, and MRI also more accurately reflects SIJ structural bone damage than X-ray [14].

The Assessment of SpondyloArthritis International Society included MRI into the classification criteria as an important tool for the early diagnosis of active sacroiliitis [3]. In the literature, the detection of BMO/O in patients with sacroiliitis has been accepted as an indispensable finding of active inflammation and has been described as hyperintense signal changes on STIR and fat-saturated T2W (FS-T2W) sequence images on MRI [15].

Previous studies have emphasized that DCE-MRI improves sensitivity for the diagnosis of acute inflammatory lesions, reflecting the vascularity and perfusion characteristics of the disease, compared with the conventional sequences recommended according to the ASAS protocol [15,16]. In our study, there was no bone marrow oedema finding that could be detected in other sequences but not in the STIR sequence. Only 4 of the patients with bone marrow oedema in the STIR sequence did not interact with the contrast agent. Although, being BMO is the most important and common MRI feature of acute sacroiliitis, its specificity is the lowest of all features, as reported by Jans et al. So, careful assessment is fundamental to avoid false-positive MRI reports [17]. Muche et al., reported BMO on FS-T2W and STIR sequences and articular contrast enhancement on postcontrast FS-T1W images were as activation criteria, but they already observed enhancement in all joints with oedema, and articular contrast enhancement was more sensitive as an indicator for activation compared to BMO, as well [18].

Therefore, there are numerous studies highlighting the importance of DCE-MRI in detecting the disease in early stages. Otveen et al., reported that early sacroiliitis could be detected on DCE – MRI while any morphological finding could not be seen on conventional radiography [19]. Also, Althoff et al., showed that DCE – MRI was useful to provide maximum diagnostic confidence in early sacroiliitis patients [20].

Other MRI features indicating active inflammation include enthesitis and synovitis/capsulitis. The latter can only be shown after contrast administration. Furthermore, advanced MR applications such as DCE-MRI and DWI, increase the sensitivity of MRI in the evaluation of disease activation [21,22].

In a study published by Gaspersic et al., both DWI and DCE-MRI were shown to be effective in measuring inflammatory changes during the treatment of ankylosing spondylitis [23]. In our study, results were indicated that differentiation of early acute SpA from chronic SpA could be possible by assessing the degree of contrast enhancement, TSI curves, and ADC measurements with DCE-MRI and DWI. So, our study is one of the few studies investigating the diagnostic performance of advanced MRI applications such as DWI and DCE-MRI in the detection, quantification and staging of early/acute SpA, also its correlation with laboratory findings namely ESR and CRP.

Bollow et al., reported that there was a significant difference in contrast enhancement intensity varying with the stage of the disease [24]. Congruous with this observation, we found that patients with acute SpA had higher F_{enh} values than ones with chronic SpA. Additionally, TSI curves of acute SpA patients were predominantly as Type 2 and Type 3.

In our study, similar to previous studies, as in the study of Şahin et al., we found that BAO was in larger areas in patients with chronic SpA than in patients with acute SpA [25]. We think this finding may help to stage the activity of the disease, together with the features of contrast enhancement and ADC values.

Diffusion-weighted imaging becomes a good option with rapid sequences for evaluating SIJs. ADC is a quantitative parameter calculated from diffusion-weighted images. It combines the effects of water diffusion and capillary perfusion in the extracellular–extravascular space, allowing quantification of inflammatory lesions. A local increase in water movement due to BMO results in increased diffusion, and measurement of high ADC values [9]. Bozgeyik et al., found higher ADC values in patients with axial SpA compared to the patients with mechanical lower back pain in the effected sacral and iliac regions [26]. Consistent with the literature, we measured higher ADC values from the areas of BMO.

Diffusion-weighted imaging is a sensitive method that can be used in the early diagnosis and follow-up of acute inflammatory lesions of the SIJs. The ADC values of patients with active sacroiliitis were measured to be significantly higher than those with chronic sacroiliitis in our study. Our results were similar to the results reported in Şahin et al.'s study [25]. The specificity and sensitivity were very high when the threshold value for ADC was set as $0.831x10^{-3}$ mm2/s.

The specificity of MRI in the detection of acute SpA was declared as 83-100% for conventional sequences, and 100% for contrast enhanced sequences in the literaature [27]. In our study, we found that the specificity values of DCE-MRI alone, DWI alone and both of their values calculated together were 87.1%, 83.9% and 90.3%, respectively. We detected only one patient with DCE-MRI, which we could not detect with DWI. So, there is a trade-off of sensitivity and specificity of different MRI features for the diagnosis of sacroiliitis in SpA, not a single feature is sufficient [17].

C-reactive protein and ESR are the laboratory parameters of inflammation. Gezmiş et al., reported that the increase in these acute-phase reactants can be used as a marker of disease activity. Furthermore, they showed a correlation between CRP values and ADC, but there was no relationship with the ESR values [27]. In another study, Puhakka et al., found that CRP values of patients with active sacroiliitis were higher in proportion to the inflammatory activity level of the disease when compared with CRP values of active SpA patients [28]. In our study, CRP values in patients with acute SpA were higher than those with chronic SpA, but we did not detect a correlation between CRP values and ADC.

Study limitations

This study has some limitations; such as relatively few patients, especially in the acute SpA group, being a single-center study, and not performing laboratory tests on the day of MRI.

Conclusion

Maagnetic resonance imaging is the leading modality for the diagnosis and classification of SpA as it showes both the active and structural aspects of sacroiliitis. It is a crucial imaging technique that was included into the classification criteria as an important tool for early diagnosis of active sacroiliitis by ASAS. DCE-MRI and DWI are advanced MR techniques that enable quantitative measurement of acute inflammation that have great importance in the diagnosis of early-stage SpA. Their combined use is superior to one alone in the diagnosis of early sacroiliitis, thus, it provides a chance for early treatment to avoid morbidity.

Compliance with Ethical Standards

Ethical Approval: The study was approved by the Haydarpasa Numune Training and Research Hospital Ethics Committee (17.03.2014, 2014/18). Informed consent was obtained from all patients prior to examination.

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Conflict of Interest: There are no conflicting interests.

Author Contributions: SAA : Design and conceptualization of the study, recruiting the patients, support for method, technique and service, evaluation of the data, writing of the article .

HG: Recruiting the patients and collecting study material, obtaining and analyzing the data, writing of the article.

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Parental perception on pediatric ambulance calling

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ABSTRACT

Objective: In this study, it was aimed to analyze the complaints of patients at presentation to Pediatric Emergency Department (ED) via 112 ambulance and the relationship between complaints and age.

Patients and Methods: Patient demographics, clinical characteristics, ED presenting complaint, definitive diagnosis requiring hospitalization, month or season of the year at the time of presentation, nationality, age, type of arrival were collected. The reason for calling the ambulance were asked to the parents. The relationship between age and triage areas were evaluated.

Results: The most common complaints at presentation included abdominal pain, nause-vomiting, high fever and seizure. Most of the patients were categorized as yellow area patients among different triage areas. The frequency of 112 ambulance calls with complaints of fever was significantly higher in the 0-2 and 2-6 age groups ($p<0.001$). The complaints of abdominal pain and nausea-vomiting were significantly higher in the age group of >10 years ($p<0.001$). The frequency of 112 ambulance use was significantly higher among refugees when compared to local residents ($p<0.0001$).

Conclusion: It was found that fever in younger age groups and the abdominal pain and vomiting in older age groups alerted families to call an ambulance. Educating parents about the appropriate use of Emergency Medical Service would make the system more efficient.

Keywords: Pediatric emergency, Ambulance, Child, Emergency Medical Service (EMS)

1. INTRODUCTION

An emergency medical service (EMS) is a service providing out-of-hospital acute care and transport to definitive care, to patients with illnesses and injuries which the patient believes constitute a medical emergency. EMS encompasses many areas of emergency care, including the triage, evaluation, management, and transport of patients from the scene of an injury or illness to their arrival at an emergency care facility (the out-of-hospital or pre-hospital care), as well as the management within the emergency department (ED) [1,2].

In 1991, European Union combined pre-hospital EMS under a single call number, "112", in all member and candidate countries. Our country is one of the countries which implemented this rule. Patients can call 112 EMS and request an ambulance in critical situations and emergencies. In our country, it is a legal liability for 112 ambulances to attend when they are called [3].

Pediatric Emergency Department can admit patients in outpatient setting as well as those who call 112. Contrary to adults, it is thought that in the pediatric age group, the knowledge level of the families, panic about the disease, socio-economic status play an active role in calling an ambulance. The reason for calling an ambulance seems to be non-emergent situations in most cases [4,5]. The ambulances are occupied unnecessarily, resulting in delays in emergency situations that require immediate intervention. This leads to increased morbidity ve mortality rates.

In this study, it was aimed to reveal the demographic characteristics, distribution of the complaint, distribution of

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the diagnoses according to triage areas, and the relationship between diagnosis and age range in patients who called 112 ambulance. Additionally, to increase awareness about the use of 112 ambulance services was a secondary goal of this study. Also, we assessed the differences in 112 ambulance call frequencies between local residents and refugees.

2. PATIENTS and METHODS

Study Design

In this study, we retrospectively analysed pediatric patients younger than 18 years old who were admitted to the pediatric EMS of Kayseri City Hospital via 112 ambulances between January 1, 2019 and December 31, 2019. The study was approved by Kayseri City Hospital Ethics Committee (2020/06/90).

Study Setting and Population

This study was conducted in Kayseri, 15th largest city of Turkey with a population approaching to 1.5 million. There were two pediatric EMS in the city: The City Hospital and the University Hospital. Transportation of pediatric emergencies to the City Hospital is most commonly provided by 112 ambulance services as part of the Public Health Services organized by the Ministry of Health in Turkey. Anyone can use an ambulance service free of charge by calling 112 and can access to pre-hospital EMS by the dispatch operators at dispatch centers in Kayseri Provincial Health Directorate. The cases were selected among the patients younger than 18 years old who arrived to Kayseri City Hospital by an ambulance. Trauma patients were not included in the study. Trauma patients must apply to the Trauma Section in adult EMS. Since, the city hospitals demonstrate the general functionality and structure of the Health System in Turkey at the highest level, this data can be applied across the country. Also, it should be noted that refugee applications are only made to the city hospitals.

Study Protocol

All patients' complaints and the International Classification of Diseases (ICD) codes were obtained from Kayseri City Hospital database for the study. Patients were evaluated in terms of demographic characteristics, month of admission, residency, nationality, the relationship between age and complaints, triage areas, type of Emergency Department (ED) arrival such as by 112 ambulance or private hospital ambulances. The patients were classified according to the national triage system [2]. In this triage system, while the black area represents deaths, the red area represents life-threatening cases that require synchronous, acute assessment and treatment with rapid action. While the yellow area represents potentially life-threatening cases with significant mortality and risk for organ loss, the green area represents cases with common health problems and stable general health status, which may be treated in an outpatient setting. The triage nurse performed the triage. The most common complaints (abdominal pain, nausea and vomiting, fever, seizure) of patients who arrived via ambulance were identified and analyzed separately. All other diagnoses were grouped together and evaluated as other complaints. The diagnoses in "other" group included constipation, conjunctivitis, iron deficiency anemia, common cold, ichthyosis, dysmenorrhea, sore throat, fatigue, myalgia, intestinal flatulence and routine pediatric control which do not require the use of an ambulance. The complaints were compared across age groups including 0-2 years, 2-6 years, 6-10 years, and >10 years. The association between the triage areas and the age groups, gender and seasonal difference was assessed. Intensive Care Unit and Surgery Service hospitalizations were examined. The differences in 112 EMS call frequencies between local residents and refugees were also evaluated.

Statistical Analysis

Data were analyzed using SPSS Statistics (IBM Corp., Armonk, New York, USA). Descriptive statistics were presented as count (n) and percent (%). The difference in 112 EMS call frequencies according to gender was determined using single sample binomial test; whereas the difference based on month and season of admission was determined using single sample Chi-square test. Fischer's exact test in RxC contingency tables was used to compare categorical variables among groups. When statistical significance was detected in Chi-square test, the intergroup difference was identified using two proportion Z test with Bonferroni correction. A p value<0.05 was considered as statistically significant.

3. RESULTS

It was found that the total number of pediatric ED admissions to Kayseri City Hospital was 296.850 per year. In the same period (January-December 2019), 3883 cases arrived in the pediatric ED by 112 ambulance (1.3%). In total, 30 patients without a diagnosis were excluded and 3853 patients were enrolled in the study.

Of the cases arrived by the ambulance 51.9% were boys, and 48.1% were girls. 98.9% of the patients arrived by 112 ambulance, while 0.9% arrived by private hospital ambulances. When the residency was considered, it was found that 96.6% of the patients were transferred from our province, followed by neighboring cities.

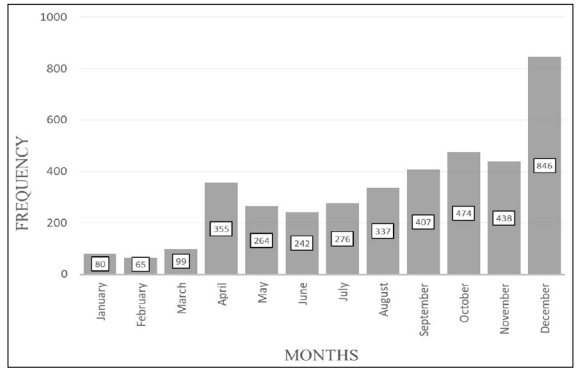

Figure 1. *Frequency of Patients According to Months*

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When 112 EMS call frequency was assessed in terms of season, the highest frequency was observed in winter (36.8%), while the lowest in spring (18.5%). Although, the presentations in winter was found to be relatively higher, it was observed that 846 patients (21.8%) presented only in December. When the distribution was assessed with respect to the months, the high number of the admissions was also detected in September, October, and November. The lowest 112 ambulance call frequency was found in February (1.7%; Figure 1).

The most common complaint for calling an ambulance was abdominal pain (11.7%); followed by nausea-vomiting (7.3%), fever (7.2%) and seizure (4.8%) (Table I).

Table I. *Distribution of main complaints for calling ambulance*

Complaints	*n*	%
Abdominal Pain	454	11.7
Nausea and Vomiting	284	7.3
Fever	278	7.2
Seizure	187	4.8
Others	2650	69.0
Total	3853	100

When compared according to age groups; the patients aged >10 years comprised the largest group (34.1%), followed by those aged 0-2 years (20.0%) and those aged 6-10 years (17.7%). There was a statistically significant association between age and complaints (Table II). The frequency of 112 ambulance call with a complaint of fever was significantly higher than other complaints in 0-2 and 2-6 age groups (p<0.001). The frequency of 112 ambulance call with a complaint of abdominal pain and nausea-vomiting was significantly higher than fever and the remaining complaints in >10 age group (p<0.001) (TableII).

Regarding the triage areas, admission to the yellow area was the most common admission type (40.28%); followed by green area (35.17%), red area (24.52) and black area (one case, 0.03%). The number of patients admitted to green area was significantly higher in winter compared to other seasons. Green area rates were comparable across spring, summer and autumn (Table III).

Based on the single sample binomial test, the rate of 112 ambulance use was significantly higher among refugees compared to the residents (p<0.0001).

Definitive diagnosis requiring hospitalization in intensive care, pediatric surgery and other services were detected (Table IV).

Table II. *Comparison of main complaints in terms of age groups*

	Seizure		Fever		Nausea and Vomiting		Abdominal Pain		Other		Test Statistics*	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	χ^2	*P*
AGE GROUPS												
0-2 years	108	63.6^{ac}	141	50.7^{a}	88	31.0^{c}	29	6.3^{b}	899^{c}	33.9^{c}	325.189	<0.001
2-6 years	34	18.2^{ac}	70	25.2^{a}	45	15.8^{c}	39	8.6^{b}	389^{c}	14.7^{c}		
6-10 years	32	11.2^{a}	43	15.5^{a}	64	22.5^{b}	125	27.5^{b}	431^{a}	16.3		
> 10 years	13	7.0^{a}	24	8.6^{a}	87	30.6^{c}	261	57.5^{b}	931^{c}	35.1		
Total	187	100	278	100	284	100	454	100	2650	100		

**Chi-square test; a, b, c indicate differences in complaints among groups.. Complaint groups having the same letter are statistically comparable.*

Table III. *Comparison of demographic data according to triage areas*

	TRIAGE AREA						Test Statistics	
	Green		Yellow		Red			
	n	(%)	*n*	(%)	*n*	(%)	χ^2	*P*
Age Groups								
0-2 years	545	86.4^{a}	331	53.1^{a}	396	60.4^{abc}	343.291	<0.001
2-6 years	263	45.6^{a}	148	25.6^{a}	166	28.8^{bc}		
6-10 years	229	33.6^{b}	319	46.8^{b}	134	19.5^{ad}		
> 10 years	318	24.1^{c}	754	57.0^{c}	250	18.9^{d}		
Gender								
Boy	765	38.2^{a}	749	37.4^{a}	489	24.4^{ab}	19.807	<0.001
Girl	590	31.9^{b}	804	43.5^{b}	456	24.6^{ab}		
Season								
Winter	588	41.6^{a}	501	35.4^{a}	326	23.0^{a}	51.616	<0.001
Spring	214	30.0^{b}	295	41.2^{ab}	205	28.8^{b}		
Summer	262	30.9^{b}	363	42.9^{b}	222	26.2^{ab}		
Autumn	291	33.2^{b}	394	44.9^{b}	192	21.9^{a}		

**Chi-square test; a, b, c indicate differences in triage area for each group. Triage area groups with the same letter are statistically comparable.*

Table IV. *Definitive diagnosis requiring hospitalization*

	n	%
Pediatric Intensive Care Unit Inpatient	211	23.0
Surgical Pathology	123	13.5
Service	580	63.5
Respiratory	151	16.5
Neurology	150	16.4
Hematology	35	3.8
Cardiology	35	3.8
Nephrology	5	0.5
Gastrointestinal	185	20.2
Newborn	28	3.1
Metabolic	4	0.4
Endocrine	6	0.7
Allergy	10	1.1
Infection	108	11.8
Intoxication	188	20.6
Psychiatric	4	0.6
Urogenital	5	0.5
Total	914	100

4. DISCUSSION

Misuse of EMS and EDs is a common problem in developing countries. In this study, the rate of patients admitted to pediatric ED by 112 ambulances was found as 1.3% annually.This rate was 5% and 7% in two different hospitals in the USA [6]. In a multicenter study from 9 hospitals in Turkey, it was reported that total number of children arriving to a pediatric ED by an ambulance was 2094 [7]. In our study, 3883 visits to a single center within a year indicated the workload of Kayseri City Hospital in the medical environment of Turkey.

Of the cases arriving with 112 ambulances, 51.9% were boys and 48.1% were girls. It is thought that this could be due to the value placed on boys by the patriarchal structure in our country. It is realized that in Turkey, girls have always been more disadvantageous than boys in many fields since their birth [8,9].

In the current study, when 112 ambulance call frequency was assessed in terms of seasonality, the highest frequency was observed in winter (36.8%), while the lowest in spring (18.5%). It is thought that severe climate conditions in winter increases the rate of EMS calls due to the challenges in transportation. Besides, another factor could be the higher incidence of upper respiratory tract disorders and fever during winter. In spring, the incidence of these disorders decrease and hence the rates of EMS calls decrease and admissions to outpatient settings increase [10,11].

Poryo et al., determined that three most common causes for requesting an ambulance were related to the central nervous system (30.6%), respiratory system (14%) and trauma (13.2%) [12]. In this study, two of the three most common complaints were related to gastrointestinal system, including abdominal pain and nausea-vomiting (19%). It was thought that the rate of 112 EMS calls was higher in abdominal pain and nausea-vomiting since it is difficult to distinguish appendicitis from non-surgical abdominal pain such as gastroenteritis and viral syndromes in younger children [13]. In our study, fever was the third common complaint and it seems that the majority of cases with fever were related to upper respiratory tract infection. Febrile convulsions were typically seen in cases having fever exceeding 38°C among 6 months old – 5 years of age [14]. When the EMS calls for fever was assessed in terms of age, it was seen that EMS call rate was higher in age groups of 0-2 years, compared to the other age groups. Thus, it was thought that calling ambulance for fever could be associated with the fear of convulsion. It has been considered that ambulances were mostly called due to the diseases of infancy, diseases that worsen rapidly, and diseases that may have serious consequences quickly [15-17]. Similar to our study, in a study by Miller et al., it was found that ambulance use was higher in children aged<1 year than those aged 5-9 years [10].

When age groups were assessed, it was seen that the ambulance was called most commonly for patients aged>10 years (34%); followed by the age group 1-2 years (20%) and 6-10 years (17.7%) . The higher rate of EMS calls in 1-2 year age group than 6-10 year age group may be attributed to the fact that disease severity was higher in the younger age group, terrifying the parents [18,19]. A study which was conducted in the USA, reported that 59% of children under the age of 15 years went to a hospital via ambulance with higher-level of pediatric resources [20]. This result supports our results.

When patients were assessed according to triage areas, the higher rate of yellow (40.2%) and green areas (35.1%) compared to red areas was linked to the perception that it is easier and more simple to access healthcare in the emergency department in our community, thus leading to unnecessary use of EMS system. In this study, it was seen that 35.1% of patients were green area patients who could be treated in outpatient setting. Again, it was found that diagnoses in the yellow area could be managed in daycare outpatient clinics. The diagnoses in "other" group included constipation, conjunctivitis, iron deficiency anemia, common cold, ichthyosis, dysmenorrhea, sore throat, fatigue, myalgia, intestinal flatulence and routine pediatric control which do not require the use of an ambulance. This suggested that EDs are used as "evening outpatient clinic" after five o'clock p.m. in our country. The higher rate of patients admitted to green area may be attributed to increase in the incidence of upper respiratory tract infection in winter. In previous studies, it was shown that the workload increased in ED in seasons when respiratory virus peak was observed [21,22]. The lower rate of admission to ward and intensive care unit admission and the fact that majority of patients were treated in outpatient basis indicated unnecessary ambulance use. In a study by Saz et al., in support to our findings, unnecessary use of EMS reached up to 90% in Turkey [7].

According to the 2007 report released by International Organization for Migration immigrants constitute 3% of the global population [23]. The challenges in access to healthcare

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services in daycare outpatient clinics make refugees dependent to ED. In previous studies, it was shown that ED admissions increased among refugees due to the their language problems [24]. It was thought that higher frequency of EMS call among refugees may be attributed to the causes mentioned above. The lack of primary care and increased incidence of illness may account for this reliance on EMS transport [25]. Future studies are required to examine the demografic and socioeconomic factors that play a role in the increased EMS utilization rate among the refugees.

Limitations

The study has some limitations. Firstly, this study presents a single center experience. The long list of diagnostic codes entered into the system, and the multiple selections of the most appropriate diagnoses were some of the restrictions of this study. Due to the retrospective design of the study, patients with missing ICD codes were excluded. Also, trauma patients were not included in the study, which was another limiting factor.

Conclusion

It is well-known that the 112 ambulance system is an integral part of ED. It was found that the complaints of fever in younger age groups and the complaints of abdominal pain and vomiting in older age groups alerted families to call an ambulance. It is recommended that primary health care service providers, educational institutions, and audiovisual media should educate families and refugees for the appropriate use of ambulance.

Compliance with the Ethical Standards

Ethical Approval: The study was approved by Kayseri City Hospital Ethics Committee (2020/06/90).

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Conflict of Interest: The authors have no potential conflicts of interest to disclose

Author Contributions: FHE: Design of the study, participated in data collection, data analysis, data interpretation, literature search, generation of figures and writing the article, FT: Participated in data collection, data interpretation and literature search and drafting the article. Both authors read and approved the final version of the article.

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Original Article

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The effect of performance score, prognostic nutritional index, serum neutrophil-to-lymphocyte ratio, and thrombocyte-to-lymphocyte ratio on prognosis in non-small cell lung cancer

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ABSTRACT

Objective: Systemic inflammatory markers and nutritional status of the patients can be helpful both in identifying high-risk cancer patients and in showing the prognosis of the disease. In this study we aimed to determine the effects of nutritional status and systemic inflammatory markers on prognosis in non-small cell lung cancer.

Patients and Methods: Patients diagnosed with non-small cell lung cancer between 2015 and 2019 were analyzed retrospectively. The prognostic nutritional index (PNI), platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio(NLR) were calculated and Eastern Cooperative Oncology Group performance status (ECOG PS), and the dates of death or last follow-up were recorded. Cox regression analysis and Kaplan-Meier curves were used to analyze the effects of parameters on survival.

Results: In the study, a total of 219 patients were analyzed. 85.4% of the patients had died. At the third step Cox regression model, ECOG 3-4 (HR:2.18), PLR (HR:1.20) and PNI (HR:1.12) predicted the survival times. Patients with PNI>45 had a higher median survival (495 days) than patients with PNI<45 (314 days).

Conclusion: In order to determine the prognosis of the patients at the time of diagnosis, it is recommended to use PNI and PLR values, which can be obtained through repeated tests and evaluated at low cost, together with performance scores.

Keywords: Lung cancer, Inflammation, Nutritional status

1. INTRODUCTION

Lung cancer is the most common type of cancer worldwide. It is the leading cause of cancer-related deaths in men and women. Despite newly developed treatment methods, the 5-year survival rate in advanced lung cancer is around 10-15% [1]. Regional spread or distant metastasis is detected in most patients at the time of diagnosis [2].

It has been shown that some parameters evaluated before treatment have prognostic importance. Poor performance score, widespread stage, lactate dehydrogenase (LDH) elevation, and weight loss are considered poor prognostic factors in lung cancer. For limited-stage lung cancer, female gender, patient's age being below 70, normal LDH level, and stage 1 disease are considered good prognostic factors, while for extensive-stage lung cancer, young age, good ECOG performance score, normal creatinine and LDH levels, single metastasis site are considered good prognostic factors in lung cancer [3,4].

Studies have shown that systemic inflammatory markers can be useful both in identifying high-risk patients and in showing the progression of the disease [5]. Studies report that the patient's nutritional status and immunity are associated with tumor spread and prognosis of the disease [6]. The prognostic nutritional index (PNI) is a measure that reflects the immunological and nutritional status of the cancer patient, which is calculated by using albumin and absolute lymphocyte value [7]. The PNI was originally developed to predict mortality and perioperative complications in patients with malnourished gastrointestinal cancer. The study showed that a low PNI value is associated with a poor prognosis [7]. Later, the relationship between PNI and survival was investigated in many cancer types

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such as hepatocellular carcinoma, colorectal, breast, lung, and gastric cancers. It was shown to be correlated with treatment response and long-term prognosis [8-12].

In recent studies investigating the relationship between cancer-related inflammatory response, it has been suggested that neutrophil, B and T lymphocytes, and platelet counts play a role in tumor inflammation and immunology [13], and it has been emphasized that they are also effective in predicting the prognosis [14]. High neutrophil levels have been reported to be an indicative of mortality in metastatic melanomas [15] and renal cell carcinomas [16]. In a study conducted in patients with pancreatic cancer, it was shown that low lymphocyte count was associated with mortality [17]. By calculating the Neutrophil-Lymphocyte Ratio (NLR: Neutrophil-to-lymphocyte ratio), the prognostic feature of these two values can be used as a single indicator. A high NLR value predicts prognosis in many cancer types, including lung cancer [18]. In addition, thrombocytosis and high platelet-to-lymphocyte ratio (PLR) have been reported to be associated with poor prognosis in many types of cancer [19,20].

Our study aimed to determine the effect of PNI, serum NLR and PLR on prognosis in non-small cell lung cancer.

2. PATIENTS and METHODS

Study Population and Data Collection

Patients diagnosed with non-small cell lung cancer between 2015 and 2019 were retrospectively analyzed. We searched the demographical, pathological, and clinical features and the laboratory data of these patients from our hospital database retrospectively.

Measurements

Baseline neutrophil, platelet (PLT) count, albumin, Eastern Cooperative Oncology Group performance status (ECOG PS), and the dates of death or last follow-up were recorded from the patients' files. Albumin value and the total lymphocyte count were used for PNI calculation. (The formula of PNI: (0.005 x total lymphocyte count/per mm^3)+(10 x serum albumin value (g/dl)). The patients were grouped based on the median value as low PNI (PNI<45), high PNI (PNI >45), and high PLR (PLR>167), low PLR (PLR<167), high NLR (NLR> 1.65) and low (NLR<1.65).

ECOG PS was developed by the Eastern Cooperative Oncology Group. This scale ranges from 0 to 4; "0" indicates fully functional and asymptomatic patient, "1" symptomatic but completely ambulatory, "2" symptomatic, <50% in bed during the day, "3" symptomatic >50% in bed but not bedbound, and "4" indicates bedbound status [21]. We classified patients according to ECOG 0-2 (ambulatuary) and ECOG 3-4 (unable to carry out any work activities) in our study, according to results of an European Experts Panel [22].

Ethical approval

Ethical approval of the study was obtained from the Ethical Committee of Samsun Training and Research Hospital, University of Health Sciences, with the decision number 17-2019 BADK/3-35.

Statistical Analysis

The categorical variables were given as numbers and percentages; continuous variables with normal distribution were presented as mean and standard deviation. Survival analysis was evaluated by the Kaplan-Meier method. The relation between survival and baseline NLR, PNR, PNI, ECOG PS were evaluated. The Cox regression analysis was used for univariate and multivariate analysis with survival-related factors. The p-value less than 0.05 was accepted as statistically significant in all comparisons. IBM SPSS statistics version 22 was used to analyze the data.

3. RESULTS

In our study, the data of a total of 219 patients were analyzed. Sociodemographic and clinical data of the patients are shown in Table I, and laboratory data are shown in Table II.

Table I. *Sociodemographic and clinical features of the patient group*

		n	%
Gender	**Male**	182	83.1
	Female	37	16.9
Histological type	**Adenocarcinoma**	107	48.9
	Squamous carcinoma	61	27.9
	Non-small cell (Nonclassified)	51	23.3
Cancer stage	**Stage 1**	6	2.7
	Stage 2	26	11.9
	Stage 3	55	25.1
	Stage 4	132	60.3
ECOG status	**0-2**	66	30.1
	3-4	154	69.9
Exitus		184	85.4
Age		219	63.1±9.5
Survival (day)		184	Median 272 (min 4 – max 1845)

ECOG: Eastern Cooperative Oncology Group

Table II. *Laboratory data of patient group*

	Mean±SD (n:219)
Leukocyte (K/uL)	9.54±5.34
Neutrophil (K/uL)	7.61±3.41
Lymphocyte (K/uL)	1.81±0.91
Trombocyte (K/uL)	295.43±117.30
CRP (mg/L)	14.67±9.12
Albumin (gr/dl)	3.52±0.65
LDH (u/L)	285.65±184.32
NLR	5.89±4.87
PLR	206.44±123.22
PNI	41.51±8.81

K: thousand, NLR: Neutrophile-Lymphocyte Ratio, PLR: Platelet-Lymphocyte Ratio, PNI: Prognostic Nutritional Index

Cox regression univariate and multivariate analysis with retrospective elimination method including ECOG, NLR, PLR, PNI, and cancer stage was performed in patients who died. At the third step regression model, ECOG 3-4 (HR:2.18), PLR level (HR:1.20), PNI (HR:1.12) predicted survival times (Table III).

Table III. *Cox regression analysis with ECOG, PLR, and PNI*

	Univariable model			Multivariable model			
Variable	**HR**	**p**	**95% CI**	**Variable**	**HR**	**p**	**95% CI**
ECOG 3-4	2.31	0.001	1.63-3.26	ECOG 3-4	2.18	0.001	1.53-3.08
PLR	1.63	0.001	1.21-2.20	PLR	1.20	0.002	1.10-1.30
PNI	1.36	0.045	1.09-1.83	PNI	1.12	0.044	1.02-1.19
NLR	1.11	0.226	0.90-2.87				

CI: Confidence Interval, HR: hazard ratio, ECOG: Eastern Cooperative Oncology Group, NLR:Neutrophile-Lymphocyte Ratio, PLR: Platelet-Lymphocyte Ratio, PNI: Prognostic Nutritional Index

Analysis with Kaplan-Meier curves for PNI (Figure 1) showed that patients with PNI>45 had a median survival of 495 days (95% CI: 400-590), and patients with a PNI<45 had a median survival of 314 days (95% CI: 249-378), and a statistically significant difference was observed between the two groups (p<0.001) (Table IV).

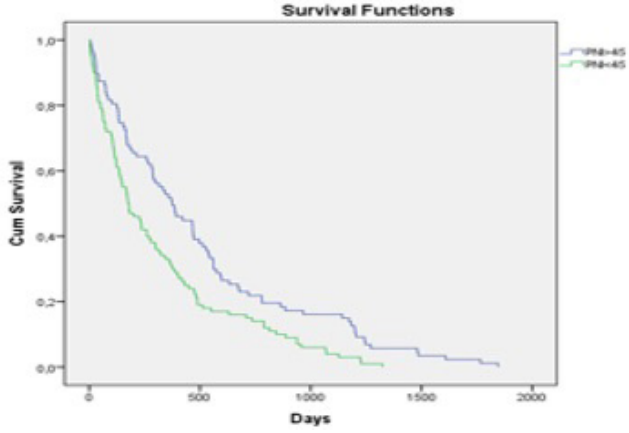

Figure 1. *Kaplan-Meier curves for survival according to median PNI (PNI: Prognostic Nutritional Index)*

Table IV. *Median survival time for PNI levels*

	Median	Std. Error	95% Confidence Interval
PNI>45	495.10	80.19	400.05-590.15
PNI<45	314.00	44.48	249.41-378.58
Overall	398.25	29.30	340.81-455.69

Log-rank (Mantel-Cox) Chi-square:10.71, p:0.001

In the analysis with Kaplan-Meier curves for ECOG performance (Figure 2), patients with ECOG 0-2 had a median survival of 688 days (95% CI: 560-815), and patients with ECOG 3-4 had a median survival of 303 days (95% CI: 247-359), and a statistically significant difference was observed between the two groups (p<0.001) (Table V).

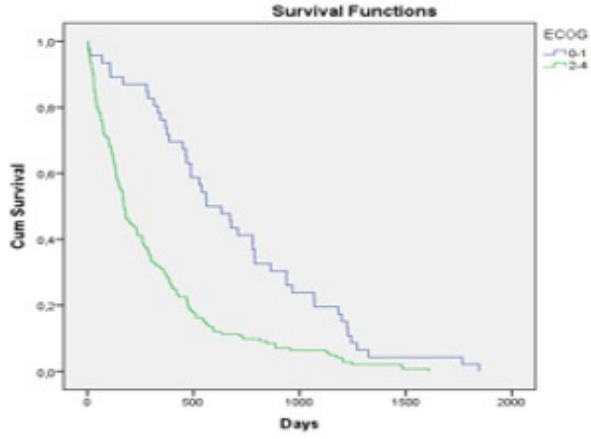

Figure 2. *Kaplan-Meier curves for survival according to ECOG performance score. (ECOG: Eastern Cooperative Oncology Group 3)*

Table V. *Median survival time for ECOG performance*

	Median	Std. Error	95% Confidence Interval
ECOG 0-2	688.00	65.09	560.53-815.68
ECOG 3-4	303.00	28.44	247.93-359.45
Overall	398.00	29.30	340.81-455.69

Log-rank (Mantel-Cox) Chi-square:23.79, p:0.001

In analysis with Kaplan-Meier curves for PLR levels (Figure 3), patients with PLR>167 had a median survival of 184 days (95% CI: 113-254), and patients with PLR<167 had a median survival of 386 days (95% CI: 277-494), and a statistically significant difference was observed between the two groups (p=0.044) (Table VI).

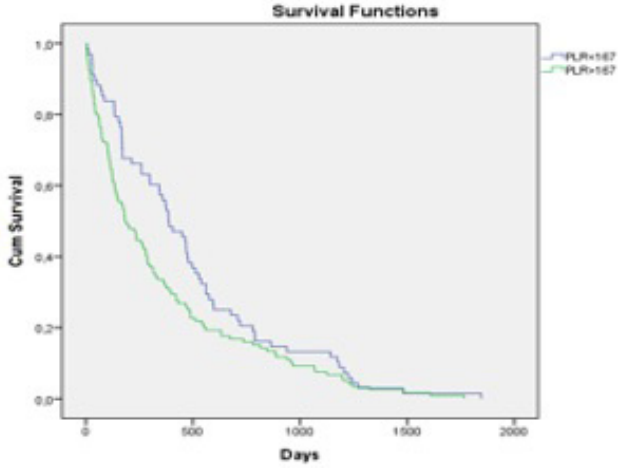

Figure 3. *Kaplan-Meier curves for survival according to PLR (PLR: Platelet-Lymphocyte Ratio)*

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Table VI. *Median survival time for PLR levels*

	Median	Std. Error	95% Confidence Interval
PLR>167	184.00	35.93	113.28-254.72
PLR<167	386.00	55.17	277.91 – 494.08
Overall	272.00	38.30	196.28-347.71

Log-rank (Mantel-Cox) Chi-square:4.07, p:0.044

4. DISCUSSION

To date, many factors have been studied to determine the prognosis of lung cancer. The values such as PNI, NLR, PLR obtained from routine biochemical data are still being utilized in the management of cancer, mainly due to their ease of application and low cost.

In our study, we evaluated the utility of PNI, NLR, and PLR in predicting the prognosis for patients followed up for non-small cell lung cancer. We found that ECOG 3-4, PLR level, and PNI survival times were predicted in the model made with the retrospective elimination method in patients who died during follow-up. Similar to our study, Hong et al. have shown that PLR and PNI values were associated with survival in non-small cell lung cancer [23].

In our study, we observed that patients with low PNI had a shorter survival time. PNI is calculated using serum albumin and total lymphocyte levels, and both values indicate the severity of chronic inflammation in the body, immunity, and nutritional status. Lymphocytopenia due to systemic inflammatory reaction is a sign of impaired cellular immunity [24,25]. A low albumin level indicates that the patient has poor nutrition [26]. Both values have prognostic significance and are known to be associated with the severity of the disease and poor prognosis [24,25]. In a meta-analysis examining the relationship between pre-treatment PNI and survival, similar to the results of our study, it was shown that patients with low PNI had worse overall survival [27]. Bekmez et al. reported that a PNI ≥45 positively affects overall survival. In addition, it was found in their study that PNI ≥45 and limited-stage disease were independent prognostic factors, and patients with PNI <45 had shorter survival [28].

It has been known for many years that poor performance scores in patients are associated with poor prognosis [29]. In a study in which patients followed up at the "National Cancer Institute" between 1973 and 1993 were examined, it was seen that ECOG performance scores of 3 and 4 negatively affected survival and were considered among the poor prognostic factors [30]. In our study, it was observed that the median survival time of patients with ECOG 0-2 was significantly higher than patients with ECOG 3-4. In the study of Torun et al., an ECOG performance score greater than one was found to be among the poor prognostic factors [31].

When we analyzed the PLR results in our study, we found that the median survival time of patients with PLR>167 was shorter than that for the patients with PLR<167. In the literature, there are conflicting results between PLR level and survival. In the study by Gu et al., which examined 3,430 patients with advanced non-small-cell lung cancer (NSCLC), a high PLR level was shown to be associated with poor survival [32]. Another study reported that PLR might be a critical prognostic risk factor in limited-stage disease [33]. However, in a study conducted with 366 NSCLC patients in 2015, PLR could not be shown as an independent prognostic factor and was reported to be linearly related to NLR [34]. In the study of Evkan Öztürk et al., on 115 patients with lung cancer, it was observed that the association between PLR value and survival was not significant [35]. In the another study, it was shown that although there is a significant relationship between PLR and overall survival, PLR is not an independent prognostic factor [23]. Despite the conflicting results in the literature, the results of our study support that PLR can be used as a prognostic factor in patients with lung cancer.

The most important limitation of our study is its retrospective nature. Since the patients' data were analyzed retrospectively, some parameters such as comorbidities, additional medications used, presence of weight loss, and treatment modalities cannot be reached for many patients. Additional prospective studies are needed to overcome this limitation.

The use of PNI, PLR, and NLR becomes important in lung cancer, where nutrition, performance, and immune status of the patients are important in evaluating the prognosis. In order to determine the prognosis of the patients at the time of diagnosis, it is recommended to use PNI and PLR values, which can be easily repeated and evaluated at low cost, together with performance scores.

Compliance with Ethical Standards

Ethical Approval: Ethical approval of the study was obtained from the Ethical Committee of University of Health Sciences, Samsun Training and Research Hospital with the decision number 17-2019 BADK/3-35.

Financial Support: No specific funding was received.

Conflict of Interest: There are no conflicting interests.

Author Contributions:YK and TT: Literature search and study design, SA and TT: Data collection, NK and YTG: Supervision and quality control and data interpretation, TT: Drafting the article.

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Comparison of the intensity of peripheral inflammation between major depressive disorder and bipolar depression by means of neutrophil-lymphocyte and platelet-lymphocyte ratios: The possible role of clinical severity and psychotic features

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ABSTRACT

Objective: The present study aimed to compare the intensity of inflammation between major depressive disorder (MDD) and bipolar disorder-depressive episode (BD-D) by using neutrophil to lymphocyte (NLR) and platelet to lymphocyte ratios (PLR) as non-specific markers for peripheral immune response, and to investigate whether and how these parameters correlate with the clinical characteristics of the depressive episodes within and between the diagnoses.

Patients and Methods: The medical records of 209 psychiatric inpatients (126 diagnosed with MDD, 83 with BD-D) and 150 healthy controls (HC) were retrospectively screened to obtain NLR and PLR values.

Results: Both MDD and BD-D presented with significantly elevated NLR and PLR compared to HC, with the increase being associated with the severity of depression but not with the presence of psychotic features. The severity of inflammation was found to be of a comparable magnitude between the two conditions, or at least indistinguishable by means of the NLR and PLR.

Conclusion: Our results suggest that both MDD and BD-D involve a presumably complex inflammatory process resulting in an observable, albeit nonspecific alteration in the distribution of peripheric blood cells. Moreover, the magnitude of the observed immune response appears to relate to the severity of the depressive episode for both conditions.

Keywords: Major depressive disorder, Bipolar disorder, Inflammation, Immune dysregulation, Neutrophil-lymphocyte ratio, Platelet-lymphocyte ratio

1. INTRODUCTION

Depression is extremely common in both community and treatment settings. Although depressive symptoms may occur in a variety of psychiatric and somatic conditions, depressive episodes are most specific for major depressive disorder (MDD) and bipolar disorder (BD), the two most prevalent mood disorders that affect up to one-fifth of people all around the world [1-3]. Several biological theories on the pathophysiology of depression have been proposed over the past decades (e.g., models focusing on neurotransmitters, neuroplasticity, genetics, circadian rhythm etc.). However, no single mechanism that is relevant to all types of depression has yet been identified, which underpins the complex and multi-dimensional etiology of the phenomenon. As with other complementary models, growing evidence also points out that immune dysregulation may be a crucial factor contributing to the pathophysiology of depression in both MDD and BD [4, 5]. Within this "immune-inflammatory" framework, the emphasis of the previous research has largely been put on the complex interplay between the neuroendocrine and immune systems [6]. Accordingly, it has been suggested that, during depression, the activation of the inflammatory response system together with the immune-regulatory pathways results in an increase in the levels of acute phase proteins such as haptoglobin [7], transforming growth factor (TGF)-β1, IL-10, as well as the activated M1 macrophage, T helper and T regulatory cells [8-10]. Many other pro-inflammatory cytokines have also been shown to be elevated in depressed patients compared to healthy controls (HC), including C-reactive protein (CRP), soluble interleukin-2 and interleukin-6 receptors, soluble tumor necrosis factor receptor, soluble p-selectin receptor, monocyte chemotactic protein-1, etc. [6, 11, 12].

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Among this plethora of available inflammatory markers, recently described neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) stand out as relatively simple and inexpensive indices of the systemic inflammatory response. NLR has been repetitively tested as a candidate parameter for systemic inflammation in neuropsychiatric disorders such as Alzheimer's disease [13] and schizophrenia [14, 15]. A few studies also attempted to examine peripheral inflammatory response in mood disorders by means of NLR and/or PLR, with their findings collectively suggesting that MDD [16], as well as different mood episodes of BD [17] are associated with increased NLR and/or PLR compared to HC. On the other hand, some other studies addressing the relationship between clinical severity of MDD and NLR-PLR provided rather inconsistent findings [18, 19].

Taken together, a substantial body of evidence indicates that the elevated inflammatory signaling is a potential mechanism that is involved in the pathophysiology of depression. However, it remains largely unclear whether MDD and bipolar disorder-depressive episode (BD-D), two distinct clinical conditions with highly overlapping symptomatology, present with differential patterns of inflammatory responses. Only a handful of studies to date have attempted to investigate the potentially distinctive features of the inflammatory profiles between the two disorders, by directly comparing depressed patients diagnosed with MDD or BD-D [6, 20, 21]. Moreover, most of the available research on the relationship between inflammatory processes and mood disorders suffer from substantial limitations such as the lack of control groups, unreliability of the diagnoses (which are mostly based on the use of questionnaires), not taking into consideration the clinical features of the depressive episodes, or relying upon cross-sectional assessments based on relatively narrow DSM criteria without further corroboration.

With these methodological shortcomings taken into account, our first objective in the present study was to assess and compare the intensity of peripheral inflammation between MDD and BD-D by using NLR and PLR as non-specific markers for the systemic immune response. Our second objective was to investigate whether and how the observed values for these markers were related to the main clinical features of the depressive episodes (depression severity, presence of psychotic features) both in MDD and BD-D. To the best of our knowledge, no prior studies have directly compared the inflammatory profiles between MDD and BD-D patients by means of NLR-PLR, or by taking into consideration the main clinical characteristics of the depressive episodes.

2. PATIENTS and METHODS

Participants

In this cross-sectional study, the database of our psychiatry inpatient clinic has been retrospectively screened for adult patients (>18 years old) who had been admitted to the hospital between 2015-2020, with a main diagnosis of MDD or BD-D. To reduce diagnostic heterogeneity, patients with psychiatric comorbidities or differential diagnoses (anxiety disorders, somatoform disorders, alcohol and substance use disorders, dissociative disorders, schizoaffective disorder, borderline personality disorder, etc.) have been excluded from the study sample. Additional exclusion criteria were the medical comorbidities that might affect inflammatory parameters (autoimmune or inflammatory diseases etc.), hepatic or renal failure, blood dyscrasia, ongoing infection, obesity (BMI >30 kg/m^2), and treatment with anti-inflammatory medications by the time of the admittance. Accordingly, the final sample consisted of a total of 209 eligible subjects, with 126 being diagnosed with MDD, and 83 with BD-D.

Aside from these two major diagnostic groups, participants have further been classified in relation to the clinical severity of their depression (moderate, severe) as well as the presence of psychotic features (additional specifier for severe depression). Additionally, a control group (n=150) of non-psychiatric outpatients, with no past history of psychiatric diagnosis or treatment, and similar demographic characteristics have been recruited retrospectively following the above mentioned criteria. The study protocol was approved by the Ethics Committee of Marmara University, School of Medicine (no: 09. 2019.1089).

Blood Tests

Data from the laboratory tests were obtained by retrospective screening of the medical records of the patients. As a routine, blood samples were drawn from the patients within 24 hours of their first admission to the clinic, generally around 8–10 a.m. following an overnight fasting period for at least 8 hours. Only the complete blood count (CBC) results at the time of the first admittance were taken into consideration. Accordingly, neutrophil/lymphocyte and platelet/lymphocyte ratios were calculated for each patient, using absolute counts.

Statistical Analysis

Data analysis in the present work was performed using SPSS (version 24.0). Means (M), standard deviation (SD) and percentages (%) were used to illustrate the demographic and other selected characteristics of the participants. Kolmogorov–Smirnov and Shapiro-Wilk were used to determine normal distribution. The chi-square test was used for categorical variables. Student's t-test or the Mann–Whitney U test were used to compare ordinal variables between two independent groups, Kruskal–Wallis or the one-way ANOVA were used to compare three or more groups. Analysis of covariance (ANCOVA) was used to control for covariates of interest when looking at group differences. A two-tailed $p<0.05$ was considered statistically significant.

3. RESULTS

Sample Characteristics

The sample consisted of 359 participants in total (Table I). 65.1% (n=82) of the MDD, 72.3% (n=60) of the BD-D, and 58% (n=87) of the HC were females, the gender distribution

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between groups was not significantly different (p=0.088). The mean age was 46.06 (SD=17.39) for MDD, 40.59 (SD=13.76) for BD-D, and 44.18 (SD=14.83) for HC. The age difference between groups was not statistically significant (p>0.05). The depression severity was moderate in 48.4% (n=61) of the MDD and 50.6% (n=42) of the BD-D patients. Among those with severe depression (n=106), 40% of the MDD (n=26) and 24.3% (n=10) of the BD-D additionally exhibited psychotic features during the episode. The distribution of the patients by symptom severity ($\chi2$=0.096, p=0.757), and presence of psychotic features ($\chi2$=2.73, p=0.098) were similar in MDD and BD-D groups, i.e. without statistically significant difference. Regardless of the main diagnosis, 54.9% (n=78) of the female and 41.7% (n=28) of the male patients had severe depression, among which 33.3% (n=26) and 35.7% (n=10) presented with additional psychotic features respectively. The mean duration of hospital stay was comparable (i.e., without statistically significant difference) between MDD and BD-D, with 5.45 (SD=2.97) and 5.67 (SD=2.87) weeks respectively (p>0.05).

Table I. *Sample characteristics*

Groups	Symptom Severity	Clinical Features	Gender (n, %)			Age (Mean ± SD)		Duration of Hospitalization (Mean ± SD)	
			Female	*Male*	*Total*	*Subgroups*	*Groups*	*Subgroups*	*Groups*
Healthy Controls			*87 (58%)*	*63 (42%)*	*150*		*44.18±14.83*		
Major Depressive Disorder	*Moderate*		*35 (57.4%)*	*26 (42.6%)*	*61*	*41.62±15.86*	*46.06±17.39*	*4.79±2.74*	*5.45±2.97*
	Severe	*non-psychotic*	*29 (74.4%)*	*10 (25.6%)*	*39*	*48.23±19.45*		*5.98±2.67*	
		psychotic	*18(69.2%)*	*8 (30.8%)*	*26*	*53.19±14.98*		*6.19±3.62*	
Bipolar Depression	*Moderate*		*29 (69%)*	*13 (31%)*	*42*	*37.90±12.99*	*40.59±13.76*	*5.62±2.79*	*5.67±2.87*
	Severe	*non-psychotic*	*23 (74.2%)*	*8 (25.8%)*	*31*	*43.39±13.38*		*5.59±3.26*	
		psychotic	*8 (80%)*	*2 (20%)*	*10*	*43.20±17.04*		*6.16±2.03*	
TOTAL			*229*	*130*	*359*				

Comparison between the diagnostic groups

Mean NLR values were 1.59 (SD=0.74) for HC, 2.30 (SD=1.51) for MDD, and 2.32 (SD=0.97) for BD-D group. Mean PLR values were 110.88 (SD=37.71) for HC, 135.29 (SD=62.92) for MDD, and 122.33 (SD=51.93) for BD-D group. Raw values were log-transformed using natural logarithm to obtain normal distribution (Table II). Log-transformed values are denoted with the prefix Ln.

Both LnNLR and LnPLR values exhibited a significant difference between groups even after adjusting for age and sex with ANCOVA (F=24.69, p<0.001; and F=6.02, p=0.003 respectively) (Table III). Post-hoc analyses revealed that, both MDD and BD-D presented with significantly higher LnNLR values, compared to controls (p<0.001 for both), while no significant difference was observed between MDD and BD-D (p=0.554). Regarding LnPLR values, MDD was no different from BD-D (p=0.084) but significantly higher than HC (p=0.001), whereas the difference between BD-D and HC was not significant (p=0.331).

Table II. *Mean LnNLR and LnPLR in relation to the clinical characteristics among diagnostic groups and healthy controls*

	Healthy Controls	Major Depressive Disorder					Bipolar Depression				
		Moderate	*Severe*			*Overall*	*Moderate*	*Severe*			*Overall*
			Non-psychotic	*Psychotic*	*Overall*			*Non-psychotic*	*Psychotic*	*Overall*	
LnNLR	*0.37±0.42*	*0.63±0.40*	*0.80±0.54*	*0.70±0.55*	*0.76±0.54*	*0.70±0.48*	*0.65±0.38*	*0.89±0.44*	*0.74±0.44*	*0.85±0.43*	*0.75±0.42*
LnPLR	*4.65±0.31*	*4.73±0.39*	*4.89±0.37*	*4.90±0.45*	*4.90±0.40*	*4.82±0.40*	*4.68±0.39*	*4.80±0.40*	*4.75±0.29*	*4.79±0.37*	*4.74±0.39*

Ln: natural logarithm, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

Comparison between the depressive episodes in relation to clinical characteristics

Regardless of the diagnostic groups (all patients with depression), mean LnNLR values were 0.64 (SD=0.39) for moderate and 0.80 (SD=0.50) for severe depression with the difference being statistically significant (t=-2.48, p=0.014). Similarly, LnPLR showed significant difference between groups with the mean values being 4.71 (SD=0.39) for moderate, and 4.85 (SD=0.39) for severe depression (t=-2.65, p=0.009). However, among patients with severe depression, both NLR and PLR presented with comparable values (i.e., not statistically significant) between those with and without psychotic symptoms (t=1.21, p=0.226, and t=-0.130, p=0.897 respectively).

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Table III. *Comparison of LnNLR and LnPLR in relation to clinical characteristics between the diagnostic groups*

	LnNLR		*LnPLR*	
Comparison	***Test statistic***	***p value***	***Test statistic***	***p value***
*Difference between HC, MDD, BD-D**	*F=24.69*	*<0.001*	*F=6.02*	*0.003*
BD-D vs HC		*<0.001*		*0.331*
MDD vs HC		*<0.001*		*0.001*
MDD vs BD-D		*0.554*		*0.084*
*Moderate vs severe depression (overall)***	*t=-2.48*	*0.014*	*t=-2.65*	*0.009*
*Non-psychotic vs psychotic severe depression (overall)***	*t=1.21*	*0.226*	*t=-0.130*	*0.897*
*MDD, moderate vs severe***	*t=-1.52*	*0.129*	*t=-2.34*	*0.020*
*BD-D, moderate vs severe***	*t=-2.19*	*0.031*	*t=-1.26*	*0.211*

Ln: natural logarithm, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio HC: healthy controls, MDD: major depressive disorder, BD-D: bipolar disorder-depressive episode
**Analysis of covariance (ANCOVA), **Student's t test*

Comparison between the diagnostic groups in relation to clinical characteristics

LnNLR and LnPLR values in relation to the depression severity and the presence of psychotic symptoms for both the MDD and BD-D groups are shown in Figure 1 and Figure 2 respectively.

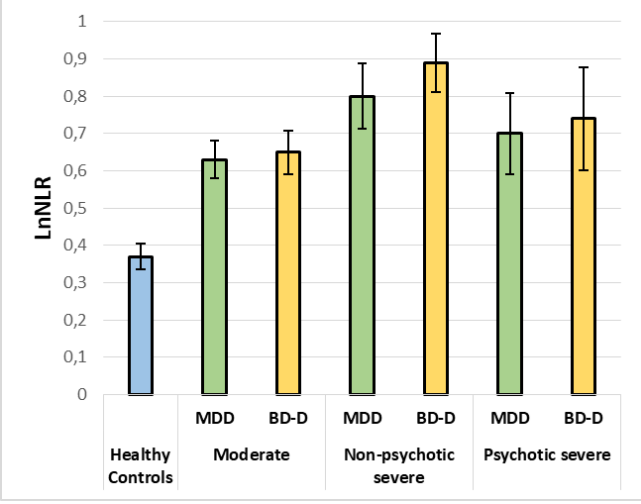

Figure 1. *Mean LnNLR values in relation to the clinical characteristics for healthy controls, patients with major depressive disorder, and bipolar depression. Bars indicate standard errors. Ln: natural logarithm, NLR: neutrophil to lymphocyte ratio, MDD: major depressive disorder, BD-D: bipolar disorder-depressive episode*

LnNLR in moderate, severe (non-psychotic) and severe psychotic depression was 0.63 (SD=0.40), 0.80 (SD=0.54) and 0.70 (SD=0.55) in the MDD; and 0.65 (SD=0.38), 0.89 (SD=0.44) and 0.74 (SD=0.44) in the BD-D group respectively. That is, severe depression without psychotic features were associated with the highest, and moderate depression with the lowest LnNLR values in both groups. Although the difference between moderate and non-psychotic severe depression was found to be significant in the BD-D (p=0.026), it did not reach statistical significance in the MDD group (p=0.87). With the psychotic features not taken into account, severe depression was again associated with significantly higher LnNLR than moderate depression for BD-D (p=0.031), but not for MDD (p=0.129).

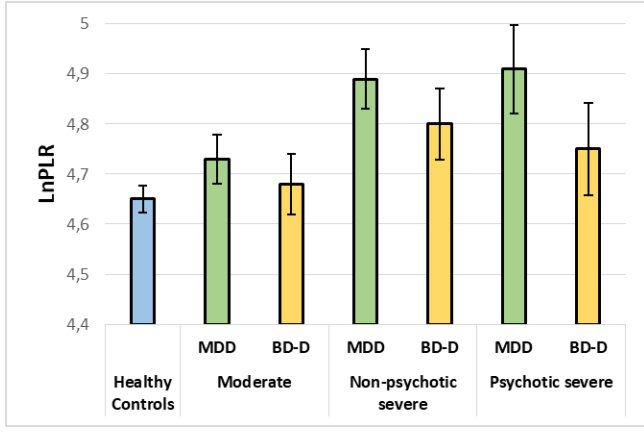

Figure 2*. Mean LnNLR values in relation to the clinical characteristics for healthy controls, patients with major depressive disorder, and bipolar depression. Bars indicate standard errors. Ln: natural logarithm, PLR: platelet to lymphocyte ratio, MDD: major depressive disorder, BD-D: bipolar disorder-depressive episode*

LnPLR in moderate, severe (non-psychotic) and severe psychotic depression was 4.73 (SD=0.39), 4.89 (SD=0.37) and 4.91 (SD=0.45) in the MDD; and 4.68 (SD=0.39), 4.80 (SD=0.40) and 4.75 (SD=0.29) in the BD-D group respectively. In contrast with LnNLR, LnPLR significantly distinguished between moderate and severe depression in the MDD (p=0.020), but not in the BD-D (p=0.21).

4. DISCUSSION

In the present study, it was aimed to compare between the intensity of the accompanying inflammation in MDD and BD-D by using NLR and PLR as non-specific indices of the peripheral immune response; and to investigate whether and how these parameters correlate with the clinical features of depression

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within and between diagnoses. Our findings showed that the two disorders presented with largely similar profiles in terms of NLR and PLR, with strikingly close mean values between the diagnoses. On the other hand, both indices presented with significantly increased values in depressed patients compared to HC, supporting the ever-growing evidence on the involvement of the inflammatory mechanisms in the pathophysiology of depression.

Although, previous research indicates that both disorders are associated with altered NLR and/or PLR [16], findings regarding the potential differences between the inflammatory profiles of MDD and BD-D are rather inconsistent. Hung et al., compared the levels of CRP, TNF-alpha, and IL-6 in a sample of patients with reactive depression, MDD, BD-D and healthy controls. Their findings revealed no statistically significant difference among the groups [22]. Similarly, Su et al., reported no significant difference in CRP, soluble TNF-R1, or IL-6 levels, among patients with reactive depression, MDD, bipolar depression, and healthy controls [23]. In their retrospective cross-sectional study, Wysokinski et al., compared CRP levels between inpatients diagnosed with schizophrenia, bipolar mania, BD-D and MD-D. Again, the authors failed to find any difference in CRP levels between the disorders [24].

On the other hand, Bai et al., compared inflammatory profiles between outpatients diagnosed with BD, MD-D and HC by means of a series of pro-inflammatory cytokines, and found that inflammatory dysregulation was more intense in BD [6]. Mao et al., attempted to explore the difference in pro-inflammatory and anti-inflammatory cytokines between MDD and BD-D by conducting a longitudinal study on a sample of outpatients with MDD (n=64), BD-D (n=61) and healthy controls (n=62). Their findings indicated that MDD and BD-D patients present with dissimilar inflammatory profiles, in terms of TNF-α and IL-13 levels in particular [25]. Finally, Brunoni et al., examined differences in immune profiles among MDD (n=245) and BD-D (n=59) patients who had depressive episode of moderate severity. The authors concluded that differences in immune profiles between BD-D and MDD patients do exist, with increased IL-10 being the primary immune-regulatory mechanism for MDD, and increased sTNFR2 and KLOTHO being the primary regulatory mechanisms for BD-D [9].

In partial contrast with these latter reports, our results pointed out that whatever the underlying immune mechanisms, the intensity of the resulting peripheral inflammation was not different between the two disorders, or at least undistinguishable by means of the NLR or PLR. On the other hand, the severity of the depression appeared to be associated with the magnitude of the increase in NLR and/or PLR in both disorders. That is, higher values were recorded for severe depression compared to moderate in both MDD and BD-D. Of note, this pattern was inconsistently reflected by the two parameters between the disorders, so that the difference was significant for NLR but not for PLR in BD-D group, whereas the opposite was true for MDD. However, the methodological framework of our study does not allow us to determine whether or not this observed relation was due to a true difference concerning diagnostic specificity between the two markers. Another striking finding of our study was that the presence of psychotic features did not seem to have any additional impact on the increase in NLR or PLR among severely depressed patients, implying that the intensity of peripheral inflammation is more closely related to depression severity than accompanying psychotic symptomatology.

Limited literature provides contradicting evidence concerning the relationship between clinical features of the depression and NLR-PLR indices. In their study conducted on MDD patients, Kayhan et al., reported higher levels of PLR in participants who had severe depression with psychotic features, compared to those with other types of depression, although this difference was not reflected in NLR [18]. In contrast, Sunbul et al., found that higher HAM-D scores in MDD patients was associated with larger increases in NLR [19]. Similarly, CRP levels and NLR were reported to be significantly higher in MDD patients with a recent history of suicide attempt compared to those without [26].

Limitations and Strengths

The present findings should be interpreted cautiously, within the methodological limitations of our study. The retrospective screening precluded us from considering several confounding factors that might have played a role in the mechanism of interaction between depression and inflammatory processes in our sample. These missing data include the exact BMI values for each patient, smoking status, age of onset of the mood disorder, number of episodes, and family history. The potential effect of the ongoing drug treatments was also discarded due to the methodological complexity related to polypharmacy; besides, only a minority of patients were drug-free at the time of admittance.

We also believe that our study has some substantial strengths to underline. First, unlike most previous studies, a high level of diagnostic accuracy was suggested to be established among the participants. The main reason for this is that, the sample consisting solely of inpatients in our clinic, the clinical diagnoses were based not on cross-sectional assessments but longitudinal and elaborate psychiatric evaluation, supported by standardized questionnaires, medical examination and comprehensive laboratory work-up. Moreover, the final diagnoses were confirmed by a thorough retrospective examination of the patients' medical records. In doing so, the inherent difficulty to cross-sectionally differentiate between unipolar and bipolar depression was suggested to have been largely overcome. Finally, we believe that the exclusion of depressed patients with psychiatric comorbidities/differential diagnoses, as well as the identification of the main clinical features of the depressive episodes have provided the possibility to delineate relatively well distinguished sub-groups with increased homogeneity.

Conclusion

Taken together, our results suggest that the pathophysiology of both BD-D and MDD involves presumably complex inflammatory processes which result in an observable –albeit nonspecific – alteration in the distribution of peripheric blood

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cells. The depressive episodes in both disorders present with significantly increased levels of NLR and PLR compared to HC, with greater values being additionally associated with severe depression, but not necessarily with the presence of psychotic features. Finally, the intensity of the accompanying inflammation appears to be comparable between the disorders, or at least, indistinguishable by means of the NLR and PLR. Given the substantial symptomatic overlap and high rate of misdiagnosis between the two disorders, researchers addressing the differential characteristics of inflammation between MDD and BD-D should not content themselves with the use of a wider range of specific bio-markers but also attempt to adopt more elaborate sampling methodologies, e.g. by enhancing diagnostic accuracy among participants through multi-dimensional clinical assessments, as well as addressing the clinical features of the depression with potential relevance (bipolar subtypes, cycling rates, family history, presence of melancholic, atypical or mixed features, etc.).

It is without a doubt that the study of inflammatory mechanisms will continue to enrich our understanding of the pathophysiology of depression. However, ranging from basic to the most sophisticated laboratory tests, biological markers are yet to be adopted as reliable diagnostic tools to differentiate between MDD and BD-D. As in the other fields of psychiatry, clinical expertise and elaborate psychiatric assessment remain the keystone of an accurate diagnosis.

Compliance with Ethical Standards

Ethical Approval: Approval for the study was obtained from the Ethics Committee of Marmara University, School of Medicine with the protocol number 09.2019.1089.

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Author contributions: Both authors were actively involved in data collection, analysis, and the writing of the article.

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Nasal fractures and anesthetic applications

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ABSTRACT

Objective: The aim of this study was to review and compare the demographic characteristics, radiological findings, pain scores and the level of satisfaction of patients who underwent nasal fracture reduction (NFR) under sedation anesthesia (SA), infiltrative anesthesia (IA) or topical anesthesia (TA).

Patients and Methods: Sixty patients were included in the study according to the types of anesthesia applied: SA group , IA group and TA group. Demographic data (age, gender, etiology, duration and time to NFR), radiological findings (presence of septal fracture, hematoma), pain scores, nasal patency and cosmetic satisfaction levels were analyzed.

Results: The mean age of patients was 23.8 ± 19.3. The mean age of females was 23 (38.3%) and mean age of males was 37 (61.7%). The mean age of the SA group was 6.1±4. The most common etiology was falls, (39 patients 65%). Duration of the operation was higher in patients (TA group) who had closed reduction. Pain score was lowest at 0 hour in the IA group (open reduction), while it was lowest at 48 hours in the TA group. Cosmetic satisfaction level was high in the SA group ($p<0.05$). Septal fracture was detected in 95% of the patients and septal hematoma in 36% of the patients in tomographic evaluation.

Conclusion: Sedation anesthesia was applied mostly to children, whereas, IA and TA were mostly applied to adult patients due to patient compliance. Short operation time and immediate pain control were advantages of IA.TA was preferred when cosmetic expectations were low in adults. Septal fracture and hematoma that cause nasal deformations, frequently seen in nasal fracture, may be missed by physical examination but can easily be detected by tomographic examination, but the risks of tomography should be noted.

Keywords: Demographic, Anesthesia, Pain, Fracture reduction, Satisfaction.

1. INTRODUCTION

Nasal Fracture (NF) is a frequently encountered emergency in daily clinical practice of the Ear, Nose Throat (ENT) and Plastic Surgery services [1], and it accounts for 39 to 45% of all facial bone fractures [2]. There are several different interventions utilized in nasal fracture reduction (NFR). These interventions are closed reduction (CR), which does not include any incision technique on one end of the spectrum, and the other one is open reduction (OR) at the other end, and this involves septoplasty and rhinoplasty techniques [3]. CR is usually carried out via blind techniques using manual manipulation or various instruments, such as the Asch and Walsham forceps. These interventions aim to fix the fractured segment of bone without direct view under the overlying mucoperichondrium [1, 4]. Although, CR generally provides acceptable outcomes, OR can facilitate better cosmetic and functional outcomes [5].

Since, NFR is a painful procedure, anesthesia is necessary regardless of CR or OR treatment [6]. Almost all types of anesthesia could be used in NFR, including general anesthesia (GA), sedation anesthesia (SA), infiltrative anesthesia (IA) and topical anesthesia (TA). These approaches result in different levels of sedation and anesthesia as a continuum from minimal sedation (anxiolysis) to moderate sedation, to deep sedation, and to complete GA [7] . In GA, the airway should be safely opened and complete loss of consciousness must be maintained;

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therefore, oropharyngeal bleeding and aspiration can be easily manipulated. In SA, intubation is not needed and there are some other advantages such as effective analgesia, adequate anxiolysis, short hospital stay and early awakening. Although, IA and TA allow to carry out surgery without the need for intubation or mechanical ventilation, anxiety-related to the procedure and the presence of some pain are their disadvantages [8]. The aim of this study was to provide an overview of NFR by examining demographic characteristics and radiological findings , pain scores and satisfaction levels in patients who underwent NFR with the use of SA, IA and TA.

2. PATIENTS and METHODS

Three hundred and twenty-five NF patients were evaluated in a secondary care hospital from 1st December 2018 to 1st August, 2020.The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and was approved by the Ethics Committee for Clinical Research at Gazi Yasargil Education and Research Hospital (REF: 2019/392). Institutional ethics committee approval was obtained before commencing to collect the data. Informed consent was obtained from all participants before NFR.

Inclusion criteria were: patients who had a computed tomography (CT) scan with head trauma or various suspicious trauma to head and face region, as well as having a radiologic evaluation only with isolated nasal trauma. Exclusion criteria were: those with additional maxillofacial trauma, those with major comorbidities (cancer, metabolic diseases, chronic diseases), those with elevated liver and kidney function tests and those with coagulation or blood disorders.

Sixty patients who underwent NFR were divided into three groups according to the types of anesthesia applied (SA, IA or TA). Each group consisted of 20 patients, and these were selected randomly. The pain scores and satisfaction levels in each group were assessed. In otolaryngological examination of 60 patients; 4 of the patients had epistaxis. Twelve patients had an overt nasal deformity and 44 patients had nasal obstruction due to deviated septum and blood clots in the nasal passages. NF type was classified with the Stranc-Robertson classification [9] (Table I). Other otolaryngological findings were found to be normal. Age, gender, cause of nasal fracture, duration of operation, reduction time, re-operation requirements were recorded from the clinical and operation notes of patients. The characteristics of the septal fracture and the presence/absence of septal hematoma were recorded by analyzing the CT of patients (Table II).

Anesthesia Procedures

In the SA group, 1.5 L/min of oxygen was administered using an oral oxygen canula. The loading dose was intravenous (IV) ketamine (1-2 mg/kg), midazolam (0.05-0.1 mg/kg), fentanyl (1-2 mcg/kg) or propofol (0.5-1 mg/kg). This administration could be increased gradually by 0.5-mg/kg [10]. In patients with low pain levels, ketamine and fentanyl were preferred. During surgery, electrocardiogram, peripheral arterial oxygen saturation and blood pressure were monitored in the operating room. In case of a decrease in oxygen saturation below 95% during surgery, spontaneous respiration was triggered by manipulation of the anesthesiologist.

The IA group received 4-6 ml of lidocaine with 1:100.000 adrenaline. This volume of anesthetic was infiltrated percutaneously over the dorsum of the nose leading to bilateral blockage of the infraorbital, infratrochlear and external nasal nerves. The nasal septum was also infiltrated in the submucosal plane. Manipulation took place as soon as the patients lost sensation.

In the TA group, the skin of the nose, ranging from the upper limits of the eyebrows and extending laterally to a vertical line passing through the infraorbital foramen, was cleaned. Thereafter, 2 g of 5% lidocaine cream (lidocream, BDderm, Istanbul, Turkey) was applied topically to the inside and outside of the nose. After waiting for the patients to report loss of sensation in the nose (around 15-20 minutes), the surgery was initiated.

Surgical Procedures and Follow-up

In the SA and IA groups, OR was applied. Hemitransfixion incision and endonasal intercartilaginous incision were carried out according to the site of fracture. Subperiosteal and subperichondrial dissections were carried out to better visualize the fractured bone or the cartilage. The septal fractures were reduced and broken nasal bones were elevated by an elevator under endoscope guidance. After reduction of septal and nasal fracture, the flaps were relocated to their original positions and incisions were sutured.

In the TA group, CR was performed. After the application of anesthesia, the nasal and septal fractures were reduced. The Walsham forceps and elevator were used as septoplasty equipment, and the handle of the scalpel was also used for manual manipulation [4]. A Doyle nasal splint was inserted to both nostrils after the operation and was removed on the third postoperative day [3]. A nasal cast was applied to keep the reduced bones intact, and the cast was removed on the eighth postoperative day.

All patients were followed up for 3 months after having NFR and contacted by telephone for the survey using a 4-point numerical scale. In follow-up visits, nasal patency and cosmetic satisfaction were evaluated by using the same 4-point numerical scale as follows 1: no or least improvement, 2: fair improvement, 3: moderate improvement and 4: maximum improvement.

Pain Assessment and Management

Visual Analogue Scale (VAS) scores at 0, 12, 24 and 48 hours after surgery, and the amount of analgesic medication required were recorded on the first and fifth days postoperatively. Pain scores were measured for all participants using a VAS from 0 to 10 (0: no pain and 10: severe intolerable pain). Children younger than 7 years of age were graded with the help of their parents. Acetaminophen was prescribed to all patients with a VAS score of ≥4 during the first 24 hours after the surgery. The patients

were discharged on the next day, and amoxicillin/clavulanate and acetaminophen were prescribed.

Statistical Analysis

All analyses were performed with the SPSS v15 software (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to determine the compliance of variables to normal distribution. Number, percentage, mean, standard deviation (SD), median, minimum and maximum values were used in the depiction of descriptive data. Since, variables did not show normal distribution, continuous data were compared with the Kruskal-Wallis test between the three groups, and post-hoc corrections for pairwise comparisons were performed with the Bonferroni method. Categorical data were compared using Chi-squared test. The threshold for statistical significance was accepted as p-value of <0.05.

3. RESULTS

This study consisted of 23 (38.3%) females and 37 (61.7%) males. The ages of the patients ranged from 2 to 88 years old, with a mean ± SD value of 23.8 ± 19.3 years. The age was significantly lower in the SA group compared to the other two groups (p<0.001), and the age was similar in the IA and TA groups (Table I). Falls was the most common etiology in all three groups (p=0.001). The median duration of operation in the SA group was significantly higher than in the other two groups (p<0.001). The median reduction time in the SA group was significantly higher than in the IA group (p=0.034) (Table I). In radiological evaluation, the incidence of septal hematoma was significantly higher in the SA group compared to the other two groups (p<0.001) (Table II).

Table I. *Demograpic characteristics of groups*

Characteristics				
	Sedation anesthesia group (n=20)	**Infiltrative anesthesia group (n=20)**	**Topical anesthesia group (n=20)**	**p**
Age	6.1±4.0, 5 (2-17)[a]	34.2±18.8, 27.5 (15.0-88.0)[b]	31.2±17.0, 25.0 (15.0-81.0)[b]	**<0.001***
Gender				
Female	7 (35.0)	7 (35.0)	9 (45.0)	0.754
Male	13 (65.0)	13 (65.0)	11 (55.0)	
Cause of nasal fracture				
Falls*	20 (100.0)	6 (30.0)	13 (65.0)	**0.001***
Assault*	0 (0.0)	9 (45.0)	5 (25.0)	
Traffic accident	0 (0.0)	3 (15.0)	0 (0.0)	
Sports	0 (0.0)	1 (5.0)	0 (0.0)	
Work related	0 (0.0)	1 (5.0)	2 (10.0)	
Duration of operation	24.5±6.3, 25.0 (15.0-38.0)[a]	12.7±3.3, 12.0 (9.0-20.0)[b]	34.1±4,7, 34.5 (29.0-45.0)[b]	**<0.001***
Reduction time (day)	3.9±2.1, 4.0 (1.0-7.0)[a]	2.3±1.4, 2.0 (1.0-5.0)[b]	3.0±1.6, 3.0 (1.0-6.0)[ab]	**0.034***
Stranc-Robertson classification				
Frontal plane 1*	10 (50.0)	1 (5.0)	4 (20.0)	**0.006***
Frontal plane 2	4 (20.0)	2 (10.0)	2 (10.0)	
Frontal plane 3	0 (0.0)	1 (5.0)	0 (0.0)	
Lateral plane 1	4 (20.0)	2 (10.0)	5 (25.0)	
Lateral plane 2*	2 (10.0)	14 (70.0)	9 (45.0)	
Committed	0	3	0	

** lines that make up the statistical difference (p<0.05)*
All data are presented as mean (± Standard Deviation).
a, b: same letters depict the lack of significant difference between the denoted groups (columns) in pairwise comparisons.

Table II. *Septal fracture and septal hematoma in radiolographic evaluation*

	Sedation anesthesia group (n=20)	**Infiltrative anesthesia group (n=20)**	**Topical anesthesia group (n=20)**	**p**
Septal fracture				
Absent	0 (0.0)	2 (10.0)	2 (10.0)	0.343
Present	20 (100.0)	18 (90.0)	18 (90.0)	
Septal hematoma				
Absent	0 (0.0)	18 (90.0)	20 (100.0)	<0.001*
Present	20 (100.0)	2 (20.0)	0 (0.0)	

** lines that make up the statistical difference (p<0.05)*

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The immediate postoperative VAS scores (0 hrs) of the group that underwent NFR with IA was significantly lower than the other two groups (p=0.001). The median VAS scores immediately after surgery in the SA and TA groups were found to be similar. VAS scores at the 12th hour (p=0.004) and the 24th hour (p<0.001) were found to be significantly higher in the SA group compared to the other two groups. In contrast, the median VAS score at 48 hours was lower in the TA group compared to the other groups (p=0.016, Table III).

The SA, IA and TA groups were found to be similar in terms of perceived satisfaction with nasal patency (p = 0.073) (Table IV).

Cosmetic satisfaction levels of the three groups differed significantly (p<0.001). Satisfaction was highest in the SA group, followed by the IA group (Table V).

Table III. *Comparison of VAS pain scores between groups immediately after surgery, at 12 hours, 24 hours and 48 hours*

	Sedation anesthesia Mean±SD Median (Min-Max)	Infiltrative anesthesia Mean±SD Median (Min-Max)	Topical anesthesia Mean±SD Median (Min-Max)	p
Postoperative at 0 hour (at PACU)	2.6±1.1 2.5 (1.0-6.0)[a]	1.5±0.8 2.0 (0.0-3.0)[b]	2.2±0.6 2.0 (1.0-3.0)[a]	**0.001***
Postoperative at 12 hours	6.8±0.7 7.0 (6.0-8.0)[a]	6.1±1.1 6.0 (4.0-9.0)[b]	6.0±0.8 6.0 (4.0-7.0)[b]	**0.004***
Postoperative at 24 hours	6.9±0.6 7.0 (6.0-8.0)[a]	5.7±0.8 6.0 (4.0-7.0)[a]	5.2±0.8 5.0 (3.0-6.0)[b]	**<0.001***
Postoperative at 48 hours	4.8±0.8 5.0 (3.0-6.0)[a]	4.9±1.0 5.0 (3.0-6.0)[a]	4.1±0.8 4.0 (3.0-6.0)[b]	**0.016***

PACU: Postanesthetic Care Unit, VAS: Visual Analogue Scale
** lines that make up the statistical difference (p<0.05)*
a, b: same letters depict the lack of significant difference between the denoted groups (columns) in pairwise comparisons.

Table IV. *Distribution of satisfaction levels of nasal patency among anesthesia groups*

	Sedation anesthesia group n (%)	Infiltrative anesthesia group n (%)	Topical anesthesia group n (%)	p
No or least improvement	2 (10.0)	1 (5.0)	1 (5.0)	0.073
Fair improvement	0 (0.0)	2 (10.0)	5 (25.0)	
Moderate improvement	3 (15.0)	3 (15.0)	7 (35.0)	
Maximum improvement	15 (75.0)	14 (70.0)	7 (35.0)	

** lines that make up the statistical difference (p<0.05)*

Table V. *Distribution of cosmetic satisfaction levels among anesthesia groups*

	Sedation anesthesia group n (%)	Infiltrative anesthesia group n (%)	Topical anesthesia group n (%)	p
No or least improvement	2 (10.0)	1 (5.0)	1 (5.0)	**<0.001***
Fair improvement*	0 (0.0)	1 (5.0)	6 (30.0)	
Moderate improvement	4 (20.0)	6 (30.0)	8 (40.0)	
Maximum improvement*	14 (70.0)	12 (60.0)	5 (25.0)	

** lines that make up the statistical difference (p<0.05)*

4. DISCUSSION

The demographic characteristics of patients with NF vary according to many factors, including geographic region, culture, religion and economic status [11]. Statistically, there was no gender-based difference in the distribution of NF. However, there was a male dominance in our study overall, similar to that reported by Chadha et al., who had a male-to-female ratio greater than 2:1. The highest incidences were seen in two age groups, in patients aged 15–30 years and in the elderly, in relation to the incidence of falls. The majority of nasal fractures in young adults were due to assault, sports and motor vehicle accidents [12]. In the hospital, which is in the South-Eastern region of Turkey, falls were the most common etiology in patients who underwent SA and TA; whereas assault was the most common cause in the IA group. In prior studies, it had been reported that assault and motor accident-related cases were more common in adults, while falls were more common in children [13]. In our study, operation time was longer in the SA group with a

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mean±standard deviation of 24.5±6.3 min because of the longer duration of anesthesia and duration of OR. In a study conducted by Kyung CR, duration of operation was 17.06 mins with SA and 20.29 mins in GA [8]. In Cook et al.'s study, either IA or blocks of the intraorbital/infratrochlear nerves, the CR surgeries took between 15-30 mins [14] and time between injury and operation was longer in the SA than IA and TA with 3.9±2.1 days in this study ($p<0.05$). The time between injury and operation was 6.8 days, according to Kim et al. [15].

Physical examination is not adequate to diagnose the complexity and details of NF. 25% of NFs that require surgery are negative in radiologic investigations. Although, CT scan can precisely show anatomic details of nasal bone and soft tissue, it carries risk for the lens of the eye especially in children [16]. In this study, CT images of the patients with NFs were evaluated in order to rule out other indications such as brain trauma as well as eye and skull trauma. Septal fractures are generally unrecognized and untreated in most of NF cases. Rhee et al., diagnosed septal fracture in 96.2% of NFs by CT examination [17]. In this study, septal fractures were present in 100% of the SA group, in 90% of the IA group and in 90% of the TA group, as determined by CT examination (Fig 1). Nasal septal hematoma (Fig 2), seen in 0.8–1.6% of NF cases is particularly more common in the pediatric population because the mucoperichondrium is loosely adherent to the underlying cartilage. Septal hematoma without any sequelae was mentioned by Alverez et al., similar to the results of the current study. We observed tomographic evidence of septal hematoma without any physical finding. It has been demonstrated that medical intervention is necessary in the presence of septal hematoma diagnosed by physical examination [18]. In this study, hematomas observed in 2 patients on physical examination were aspirated after performing a hemitransfixion incision under SA. As a result, advantages and disadvantages of performing CT should be carefully evaluated by the physician.

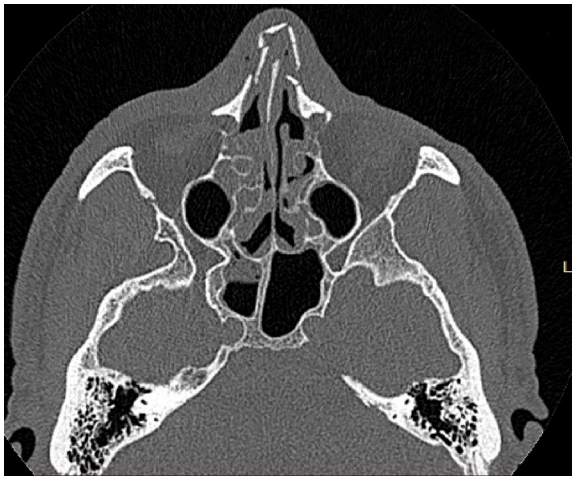

Figure 1. *CT image of a 55-year-old man after physical assault. Note nasal septal fracture and nasal bone fracture; Stranc-Robertson classification C treated under infiltration anesthesia*

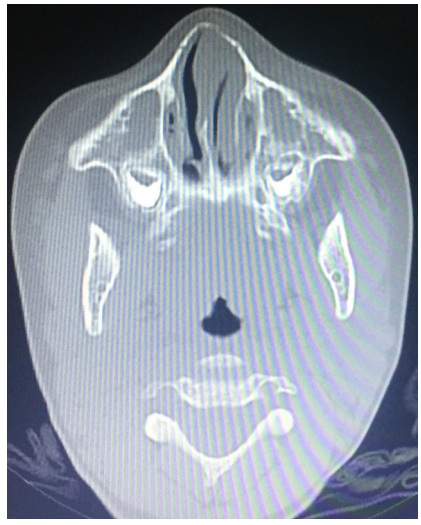

Figure 2. *CT image of a 5-year-old boy who fell down. Note septal fracture, minimal septal hematoma and nasal bone fracture. Stranc-Robertson classification F2*

Nasal fracture reduction procedures cause pain during and after surgery [19]. Atighechi et al., in their comparative study of CR procedures found that mean pain score was 2.35 in TA group, 2.47 in IA group, and 1.9 in GA group, and these were statistically nonsignificant among the groups [20]. In this current study, immediate postoperative VAS scores were lowest in the IA group (1.5±0.8). VAS scores at 12 hours were (6.8±0.7) and at 24 hours it was (6.9±0.6). These scores were found to be significantly higher than those in the SA group because OR of NF was carried out in SA group and this was expected to be more painful. In OR, septoplasty or rhinoplasty were performed to reach the septum or nasal bones for direct visualization [3]. VAS scores at 48 hours showed that pain was lowest in the TA group (4.1±0.8) as the TA group had CR. Sclafani et al,, in their study of postoperative pain in septoplasty and rhinoplasty, found that the pain reported for septoplasty was 0-78 and pain reported for rhinoplasty was 0-88 on scale of 100 by VAS scale [21]. According to a study, less pain was felt by using general lidocaine anesthesia than using topical lidocaine and lidocaine infiltration at 6 hours in CR [22].

Perceived satisfaction in NF can be affected by the type of treatment and anesthesia choice. In the past studies, satisfaction with NF performed by CR is reported as 90% [20]. Satisfaction level was 98%, 100%, and 71% in studies conducted by Ridder et al., Ondik et al., Hung et al., respectively [23,5,24]. In a study by Murray and Marran, failure rate was 32.5% and Yılmaz et al., found that satisfaction level after 6 month of CR was 65% [25]. Atighechi et al., in their comparative study of GA, IA and TA+IA in NFs, found that satisfaction among groups were statistically similar [20]. In this study, nasal patency satisfaction was similar among all groups ($p>0.05$) with maximum improvement of 75% in SA, 70% in IA and 35% in TA. In contrast, cosmetic satisfaction was significantly different between groups ($p<0.01$). Cosmetic satisfaction with maximum improvement was 70% in SA, 60%

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in IA and 25% in TA group. In a study by Rajapakse et al., there was no statistical significance between TA+IA and GA groups in terms of cosmetic satisfaction and nasal function. The study also found 86% satisfaction with nasal patency, 84% in cosmesis in either GA or TA+IA [26]. In CR under LA 78% functional satisfaction and 69.5% cosmetic satisfaction were found by Vilela et al. [27]. In this current study more favorable results in both nasal patency and cosmetic satisfaction were found in SA group because of OR (Figures 3A, 3B, 3C).

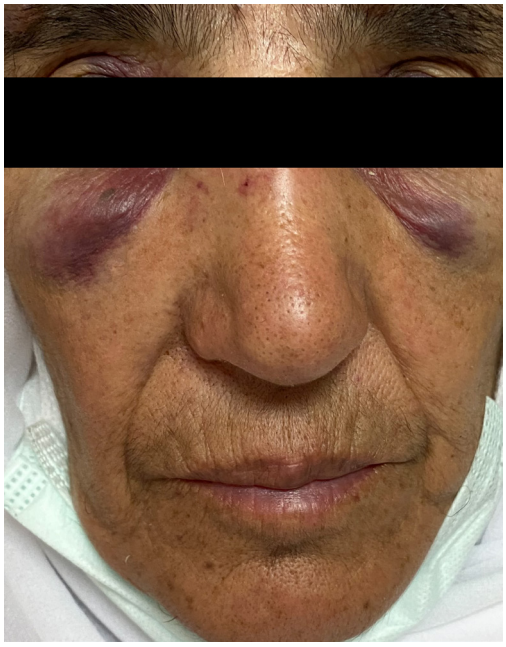

Figure 3A. *A 63-year-old female who fell down. Nasal axis deviation before she underwent CR (closed reduction) under local anesthesia*

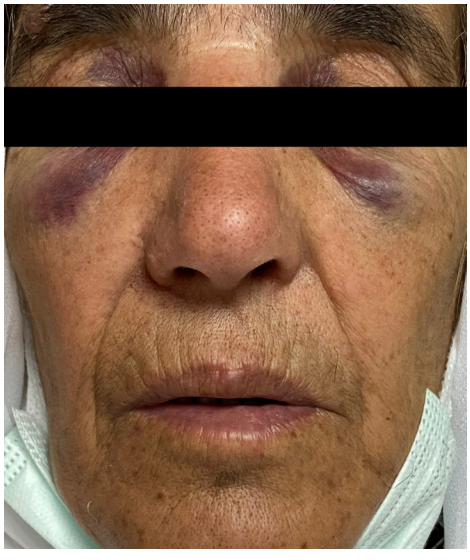

Figure 3B. *Following CR, disapperance of axis deviation*

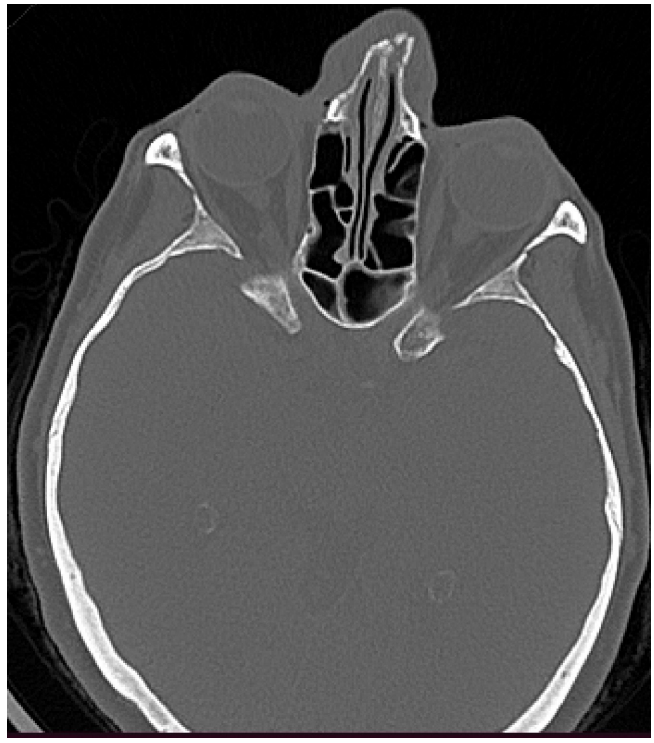

Figure 3C. *CT image with nasal axis deviation to the left before CR. Stranc-Robertson classification L2*

This current study is a descriptive study that provides an overview of daily practice in ENT clinic about NF, the demographic characteristics, level of pain and satisfaction of patients and the radiologic details of fractures. Small sample size, lack of standardization in terms of age and treatment options (CR/OR) among groups and assessment of pain and satisfaction of children by parents were limitations of this study. Although, this study provides an idea about the level of pain and satisfaction, exact evaluation of pain and satisfaction was not obtained from the results. We performed OR in the SA and IA groups, while CR was utilized in the TA group. Also, there are methodological difficulties in comparing pain and satisfaction between patients receiving TA, IA and SA. For instance, SA recipients will be unconscious during the procedure, and therefore, only post procedural pain can truly be assessed. There may also be a tendency for patients to attribute surrogate outcomes to their SA, such as pain on insertion of intravenous cannulae, splints, post-operative nausea or vomiting, or other post-operative symptoms. In accepting these limitations, we decided to provide an overview of NF treatments; OR vs CR and the level of pain and satisfaction among two treatment options with SA, IA and TA groups. However, it is rather evident that anesthesia approach and type of reduction surgeries may vary in different hospital settings, patient characteristics, and the surgeons. Other studies should be conducted with the inclusion of different settings and different properties.

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Conclusion

Nasal fractures can be efficiently and comfortably treated with SA in children. IA and TA are mostly applied in adults. Tomographic evaluation of NF provides detailed assessment especially in septal fracture and hematoma, mostly seen in children which requires surgical intervention but radiation hazards should be kept in mind. Additionally, although immediate effects on pain appear to be insufficient with TA, later pain results show favorable effects and is ideal preference when cosmetic expectation is low; whereas, immediate pain alleviation is better with IA. Cosmetic satisfaction was highest with SA in which OR was performed in our study. Although, choice of anesthesia and treatment are multifactorial depending on surgeon preference, hospital circumstances and patient characteristics, additional studies are needed to enrich the literature about NF to reach more standardized applications in anesthesia.

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Compliance with Ethical Standards

Ethical Approval: The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and was approved by the Ethics Committee for Clinical Research at Gazi Yasargil Education and Research Hospital (protocol no: 2019/392). Institutional ethics committee approval was obtained before commencing to collect the data. Written informed consent was obtained from all participants before NFR. Patients also gave their consent for images relating to their cases to be reported in a medical publication.

Conflict of Interest The author declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Case Report

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COVID-19, parvovirus and acute HIV infection in the gamut of diagnosis of fever and rash

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ABSTRACT

Coronavirus disease-19 (COVID-19) patients continue to experience different symptoms each day. Many patients were seen with common symptoms such as fever, fatigue, myalgia, respiratory symptoms (e.g., dry cough, dyspnea), smell and taste disorders, gastrointestinal symptoms, and dermatological findings. Although, fever lasting <7 days has been reported in most patients, it has been seen in patients with persistent or recurrent fever patterns in the second week of illness.

Although, any symptoms accompanying fever during the pandemic suggest the diagnosis of COVID-19, other etiologies should also be kept in mind. In this case report, we present two patients who were admitted with fever and rash were initially thought to have COVID-19 but were diagnosed with acute parvovirus infection and acute HIV infection finally.

These cases are presented to draw attention to the importance of taking a good history and making a rational differential diagnosis.

Keywords: COVID-19, Parvovirus, HIV, Fever, Rash, Cutaneous manifestations

1. INTRODUCTION

The coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spread rapidly all over the world and was declared as 'pandemic' by the World Health Organization (WHO) on March 11th, 2020 [1]. With the increase of patients worldwide, the clinical spectrum of COVID-19 is being better defined and new symptoms are noticed. Most studies in hospitalized patients reveal that the common symptoms of COVID-19 are respiratory (eg dry cough, dyspnea) with fever, fatigue, myalgia [2,3], but smell and taste disorders, gastrointestinal symptoms, and dermatologic findings have also been reported [4-6].

In the midst of pandemic, clinicians should suspect COVID-19 in every case of prolonged fever but also do not forget other etiologies. Although, fever was reported in about 72–98.6% of patients, usually lasting <7 days, there were patients who had fever persisting into the second week of illness or had a saddleback pattern of fever [7].

As the data related to COVID-19 emerged, it was observed that patients might manifest with dermatological findings such as; contact dermatitis-like itch, urticarial lesions, chicken-pox lesions, exacerbation of pre-existing skin diseases, including seborrheic dermatitis and acne, and vasculitic skin lesions [8].

Along with the current literature, COVID-19 emerged as a disease that should be included in the differential diagnosis of fever and rash. Here, we report two cases presented with fever and rash, mimicking COVID-19 with clinical and laboratory findings, diagnosed as acute parvovirus infection and acute human immunodeficiency virus-1 (HIV)-1 infection, respectively.

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2. CASE REPORTS

Case 1

A 38-year-old male anesthesiologist applied to outpatient clinics of infectious diseases with a two-day history of fever (38.7°C), fatigue, myalgia, and arthralgia on 20 March 2020. He reported dry cough without dyspnea and other respiratory complaints. He denied any history of travel and contact with a recent traveler or confirmed COVID-19 patient. On presentation, he looked clinically well and his body temperature was 37.4°C with normal blood pressure and heart rate. Physical examination was unremarkable except for decreased lung sounds at the left lower posterior chest. Chest radiography was normal. Laboratory tests revealed lymphopenia and mild thrombocytopenia. As it was influenza season, oseltamivir was commenced.

Table I. *Laboratory findings of the patients*

Measure	Reference Range	Case 1	Case 2
Hemoglobin (g/dL)	11.7-15.5	13.7	11.8
White-cell count (µL)	4100 – 10200	**3100**	4400
Absolute neutrophil count (µL)	1800 – 6400	2240	3220
Absolute lymphocyte count (µL)	1200-3600	**520**	**850**
Platelet count (µL)	159 000 – 388 000	**138.000**	212.000
Creatinine (mg/dL)	0.67 – 1.17	0.89	0.62
Blood Urea Nitrogen (mg/dL)	6-20	11.1	7.98
Alanine aminotransferase (U/L)	<50	34	**410**
Aspartate aminotransferase (U/L)	<50	37	**695**
Gamaglutamil transferase (U/L)	<38	44	**334**
Alkalen phospatase (U/L)	30-120	39	**131**
Total Bilirubin (mg/dL)	0.3-1.2	1.33	**0.90**
Creatin Kinase (U/L)	<145	62	**2935**
Lactate Dehidrogenase (U/L)	<247	178	**2951**
D-dimer (mg/L)	0 – 0.55	**1.35**	**8.07**
C-reactive Protein (mg/dL)	0 – 0.8	**6.66**	**2.84**
Procalcitonin (ng/mL)	0 – 0.1	**0.27**	**1.261**
Sedimantation (mm/saat)	0 – 20	5	17
Ferritin (µg/L)	11-307	185	**6561**

He did not defervesce under oseltamivir treatment, and he developed arthralgia at the small joints of the hands, wrists, elbows, eventually he was re-admitted for further evaluation on the 8th day of fever. He had no dyspnea and hypoxia. His body temperature was 38.4°C. Bilateral, non-pruritic, maculopapular rash was present in the lower limbs (Figure 1). There was no "slapped cheek" sign or any other facial lesions specific to parvovirus infection. He had mild tenderness with no heat or swelling at his proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints. He was capable of closing his fist totally with a normal hand grip. Laboratory tests revealed lymphopenia and mild thrombocytopenia. There was no red cell aplasia. C-reactive protein (CRP) and D-dimer levels were significantly elevated (Table 1). He was hospitalized and isolated with standard, contact, and droplet precautions as a probable COVID-19 case. Repeated SARS-CoV-2 real-time polymerase chain reaction (PCR) test results with nasopharyngeal swab were negative. A control chest computed tomography (CT) turned out normal. Transthoracic echocardiography ruled out endocarditis. An abdomen ultrasound confirmed splenomegaly of 15.5 cm.

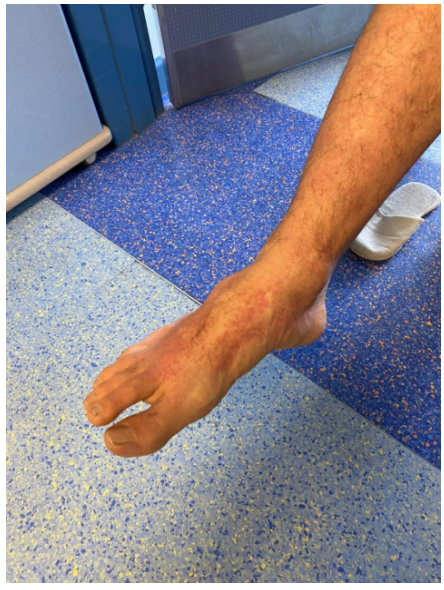

Figure 1. *Non-pruritic maculopapular rash on the dorsum of right foot*

Antinuclear anti-body (ANA) was positive at a titer of 1/160 with granular and nucleolar pattern. Double-stranded DNA (dsDNA) and extractable nuclear antigen (ENA) antibodies [anti-ribonucleoprotein (Anti-RNP), anti-Sjögren syndrome A-B (anti-SSA, SSB), scleroderma antibodies (Scl-70 and anti-Jo-1) were negative. Rheumatoid factor (RF) was 38.8 IU/mL (0-20 IU/mL), anti-cyclic citrullinated peptide (anti-CCP) and complement levels were within the normal ranges. Diagnostic criteria of any rheumatological disease was not met and rheumatology consultation ruled out probable connective tissue disorder.

Blood and urine cultures remained sterile. Extensive viral and bacterial screening, ruled out Epstein-Barr virus, cytomegalovirus, rubella, hepatitis A,B,C (HAV, HBV, HVC), human immunodeficiency virus (HIV), *Coxiella spp.*, and *Brucella spp.* infections.

A skin biopsy of the maculopapular rash was performed and reported as non-specific.

As the patient suffered from fever, malaise, arthralgia, maculopapular rash and had splenomegaly, lymphopenia and

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elevated CRP, parvovirus infection was considered. Parvovirus PCR from peripheral blood was positive at 55200 IU/ml and the patient diagnosed with parvovirus infection. Acetaminophen was ordered to alleviate symptoms. He became symptom-free after day 10.

Case 2

A 27-year-old female presented with a 10-day history of fever, dry cough, and sore throat, and rash. She was previously seen by a family physician who commenced oral amoxicillin treatment for exudative pharyngitis. On admission, her body temperature was 38.5°C, blood pressure was 90/50 mm Hg, her pulse was 112 beats per minute, respiratory rate was 18/minute, and oxygen saturation was 98% in room air. She had hyperemic oropharynx and enlarged cervical and axillary lymph nodes. Erythematous macular patches were present all over her body (Figure 2). She was hospitalized and isolated as a probable COVID-19 case.

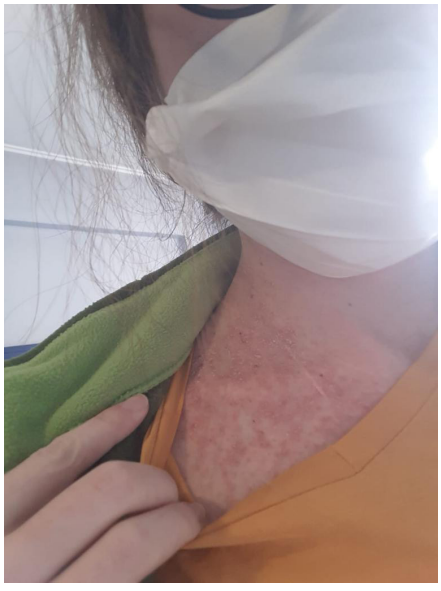

Figure 2. *Erythematous macular patches on the front of the neck*

Multiplex respiratory PCR panel and SARS-CoV-2 reverse transcriptase-PCR from nasopharyngeal swap turned out negative. Chest CT scan demonstrated normal lung parenchyma, minimal left-sided pleural effusion, and bilateral, slightly thickened axillary lymph nodes with short diameters less then 1 cm. Dermatology consultation was done for confluent erythematous macular patches fading under pressure all over her body and the patient was put on topical clobetasol 17-propionate with the suspicion of drug eruption or infectious mononucleosis.

The levels of erythrocyte sedimentation rate (ESR), CRP, procalcitonin, D-dimer, ferritin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and LDH, creatine kinase (CK) were elevated. Serological analysis indicated no infection with Borrelia burgdorferi, parvovirus, rubella, HAV, HBV, HCV, Epstein-Barr virus, and cytomegalovirus and coxiella burnetii. Anti-streptolysin titer (ASO) and RF, ANA, anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Cultures of blood and urine were negative (Table I).

Although, we could not demonstrate SARS-CoV-2 infection, oral hydroxychloroquine and azithromycin were started as endorsed by national guidelines [9]. The patient did not defervesce and her general condition remained unchanged, and for this reason favipiravir was added to the treatment regimen, and the patient was further evaluated as the fever-of-unknown origin. Cervical CT revealed bilateral multiple heterogeneous enlarged lymph nodes in cervical level 2. Abdominal CT demonstrated increased contrast-enhancement in the gallbladder wall with diffusely edematous gallbladder bed. A wedge-shaped hypodense region was observed at the level of the falciform ligament that was compatible with focal steatosis increased size and density in the left ovary, increased density of the anterior uterus, and minimal free fluid was detected at the pelvis and at the right paracolic groove. These findings were consistent with pelvic inflammatory disease (PID) and Fitz Hugh Curtis Syndrome (FHC) (Figure 3). Multiplex real – time PCR from endocervical sample turned out positive for *Mycoplasma genitalium*. Gentamycin, ceftriaxone and doxycycline treatments were started. Sexually transmitted disease (STD) screening was performed and ruled out syphilis, gonorrhea, chlamiydia, and herpes virus infections. Fourth-generation HIV enzyme-linked immunoassay (ELISA) test was positive and HIV confirmatory test revealed positive for p24 antigen but negative for anti – HIV antibodies. HIV viral load was above the detection limit (>10000000 copies/ml). Eventually, Fiebig stage II primary HIV infection was diagnosed. As soon as the patient was informed about the diagnosis, antiretroviral regimen, composed of 200 mg emtricitabine / 245 mg tenofovir disoproxil fumarate and 50 mg dolutegravir was commenced. Liver function tests started to improve with the treatment of PID and antiretroviral treatment. The patient was discharged 2 days later and is being under follow-up at the outpatient clinic of infectious diseases department.

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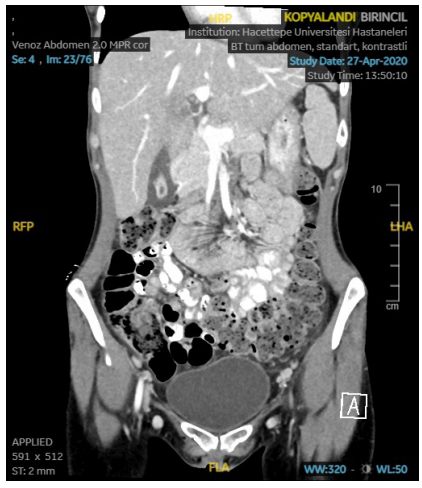

Figure 3a

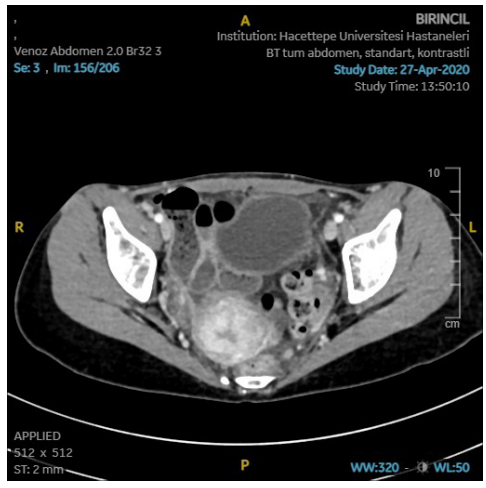

Figure 3b

Figure 3. *Abdominopelvic computerized tomography images of case 2*
3a. Increased contrast-enhancement of the gallbladder wall with diffusely edematous gallbladder bed
3b. A wedge-shaped hypodense region was observed at the level of the falsiform ligament which was compatible with focal steatosis increased size and density in the left ovary, increased density of the anterior uterus, and minimal free fluid was detected at the pelvis and at the right paracolic groove. These findings were consistent with pelvic inflammatory disease (PID) and Fitz Hugh Curtis Syndrome (FHC)

3. DISCUSSION

Here we report 2 cases who presented with COVID-19 symptoms of rash and fever, mimicking COVID-19 with clinical and laboratory features, were diagnosed parvovirus and acute HIV infection, respectively.

Diagnosing patients with fever and rash is a challenge for physicians. They need a fast and rational approach because some of these patients may be in a life-threatening situation or need isolation to reduce their potential transmission risk to others. For clinical diagnosis a complete history and a careful physical examination are essential. Epidemiologic clues are also important such as age, travel/sexual history, season, geographic location, exposures including to insects, animals and ill contacts, medications, immunizations, and history of childhood illnesses [10].

In a prospective study about clinical features and etiology of adult patients with fever and rash, the etiology were divided into three groups as infectious (50%), noninfectious (40%), and undiagnosed (10%). The most common type of rash is maculopapular, and the most common 5 causes are measles, cutaneous drug reactions, varicella, adult-onset Still's disease, and rickettsial disease [11].

Rashes are generally non-specific but have complementary importance in the differential diagnosis when other symptoms are combined with the characteristics of the rash, such as the history of medication and allergies or the social and environmental background, as well as morphology, location, and distribution [12]. In addition to basic laboratory tests, dermatology consultation and skin biopsy may be required to diagnose.

Presented patients had both fever and rash. Parvovirus and HIV are also in the differential diagnosis of fever and rash syndromes. Approximately 25% of parvovirus infected individuals will present with rash and/or arthralgias. There was joint tenderness in the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints of case 1. Joint symptoms with parvovirus are usually acute, symmetric, and most frequently involve the small joints of the hands, wrists and knees [13]. There are case reports of acute parvovirus infection-causing transient autoimmune state manifesting as the presence of autoantibodies [14]. ANA were also reactive in case 1. In the absence of a sound exposure history, we were misled toward diagnosing a connective tissue disorder. In parvovirus infection rash most commonly occurs in children, when it occurs in adults, the rash is often less characteristic.

A morbilliform rash predominantly involving the trunk has been reported as the most common cutaneous manifestation of COVID-19 [15]. Since, the patient had fever, arthralgia, rash, lymphopenia and high D-dimer we had to rule out COVID-19. Lymphopenia and/or thrombocytopenia can also be observed in parvovirus infection [16]. Since, these laboratory results are not specific, all possible infections should be kept in mind in the differential diagnosis.

The case 2 had fever, dry cough and there was maculopapular rash on physical examination. Fever is present in the vast majority of patients with symptomatic primary HIV infection. A generalized rash is also a common finding. Apart from these complaints, dry cough and sore throat also can be seen in primary HIV infection [17]. Needless to say, none of these findings is specific and COVID-19 may well have just presented with similar symptoms. Because of the wide range of symptoms

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associated with primary HIV infection, clinicians could have a low level of suspicion.

In current pandemic days, COVID-19 ranks the first in the differential diagnosis of all patients with fever plus any other symptom. Focusing only on the diagnosis of COVID-19 may cause us to skip many other diagnoses. In a proportion meta-analysis, fever (84.8%; 95% CI, 78.5% to 90.1%) was identified as the most common clinical manifestation in all COVID-19 patients [18]. Multiple skin manifestations such as exanthematous rash, pernio (chilblain)-like acral lesions, livedo-like/retiform purpura/necrotic vascular lesions, urticaria, vesicular (varicella-like) eruptions have also been described in patients with confirmed or suspected COVID-19 [19,20].

To establish the etiology of febrile illness and rash of our patients we carefully performed the evaluations, keeping in mind that fever cannot only be caused by COVID-19 but also by other common causes that are consistent through the decades, even during the pandemic.

In conclusion, in the midst of pandemic, clinicians should suspect COVID-19 in every case of prolonged fever but also do not forget other etiologies. Obtaining an accurate history and making a rational differential diagnostic work-up is more important than ever. Last but not least, COVID-19, is new and attractive, but we cannot ignore the old "ones". Keep oldies in mind.

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