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EDITORIAL

Our Dear Coleagues,

As you know, our journal is publish 6 times per a year. We are proud to publish the this fourth issue of JOMPAC in 2023. The quality of the articles is increasing day by day in our journal, which is in Ulakbim TR-Index and many international indexes. In near future, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering valuable international indexes such as SCI-Expanded, Scopus, ESCI, and Pubmed. We would like to thank all the authors who contributed to the publication of their valuable scientific articles in our journal. In addition, we would also like to thank everyone who contributed to the journal at any stage.

Sincerely

Prof. Aydın ÇİFCİ, MD
Editor in Chief

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Efficacy and safety of combined thermocoagulation radiofrequency and pulse radiofrequency in the treatment of trigeminal neuralgia

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ABSTRACT

Aims: The aim of this study was to evaluate the efficacy and safety of radiofrequency thermocoagulation (RFT) combined with pulsed radiofrequency (PRF) of the Gasserian ganglion in patients with V2/V3 trigeminal neuralgia (TN).

Methods: We evaluated 27 patients with V2/3 TN who had undergone combined RFT and PRF of the Gasserian ganglion. Patients were treated with PRF (42°C, 45 V, 20 ms, 120 s), RFT (65°C, 60 s), RFT (70°C, 60 s), and PRF (42°C, 45 V, 20 ms, 120 s), consecutively. Visual analogue scale (VAS) and Barrow Neurological Institute Pain Intensity Scale (BNI) scores were evaluated before and after (1st month, 6th month, and 12th month) the procedure. A BNI score of 1-3 was considered as an effective treatment, while a BNI score of 4 or 5 indicated unsuccessful treatment.

Results: VAS scores were significantly lower than the baseline values in all post-treatment evaluation visits (1st month, 6th month, 12th month) during the 12-month follow-up period ($p<0.001$). After treatment, 26 patients (96.2%) at 1 month, 25 patients (92.5%) at 6 months, and 20 patients (74%) at 12 months had BNI scores of 1-3. No association was found between improvement in BNI and variables such as age, gender, duration of pain, TN side, affected branch, or pre-treatment VAS scores ($p>0.05$).

Conclusion: Combined RFT and PRF to the Gasserian ganglion is a safe and effective therapeutic approach in the treatment of TN. However, its efficacy partially decreases after one year.

Keywords: Trigeminal neuralgia, Gasserian ganglion, pulse radiofrequency, radiofrequency thermocoagulation

INTRODUCTION

Trigeminal neuralgia (TN) is characterized by short-term, extremely severe, paroxysmal electric shock-like pain in the facial region innervated by one or more trigeminal nerve branches.[1] Primarily affected branches are the 2nd, 3rd and less often 1st branch in TN.[2] The prevalence of TN is 12.6-28.9 per 10 million increasing with age, and the prevalence is almost twofold higher in women.[3]

The etiopathogenesis of TN has not yet been clearly explained. According to the most accepted firing hypothesis in pathophysiology, compression or demyelination in the afferent neurons of the trigeminal root or ganglion may lead to the sensitization of neurons and cause ectopic impulses.[4]

The first-line treatment of TN is carbamazepine, and approximately 70% of patients respond to carbamazepine.[5,6] In cases where medical treatment fails, or carbamazepine cannot be used due to side effects, many other interventional methods and surgical treatments (e.g., microvascular decompression, percutaneous balloon compression, radiofrequency applications, gamma knife, and percutaneous nerve blocks) can be applied.[6]

Radiofrequency thermocoagulation (RFT) of the Gasserian ganglion is a frequently applied effective method in the treatment of TN. However, some complications such as facial numbness, masseter muscle weakness, decreased corneal reflex, dysesthesia, and anesthesia dolorosa may be seen in patients treated with RFT.[7] Pulsed radiofrequency (PRF) has been tried as an alternative treatment for TN, but controversial results have been reported.[8-12] More recently, it has been reported that low-temperature RFT (<65°C) combined with PRF may be effective in the treatment of pain without increasing complications.[13,14] However, there is no consensus on parameters such as duration of radiofrequency, temperature, and voltage for combined PRF and RFT therapy in the treatment of TN. The purpose of this study was to evaluate the effect

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of combining 120 s of PRF before and after sequential RFT at 65°C and 70°C to the Gasserian ganglion in the treatment of V2/V3 TN.

METHODS

The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 19.10.2022, Decision No: E1-22-2967). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The files of 27 patients who were treated with combined RFT and PRF to the Gasserian ganglion with a diagnosis of TN in our clinic between June 1, 2019, and August 31, 2021, were retrospectively analyzed. Since this study was conducted retrospectively, written informed consent was not required.

The inclusion criteria were V2/3 TN and treatment with combined RFT and PRF applied to the Gasserian ganglion, and had an assessment of pain and improvement with VAS at baseline, 1st, 6th and 12th months and BNI at 1st, 6th and 12th months. Patients with inadequate final needle position, patients with TN secondary to mass compression, and patients with a history of interventional procedures for TN other than radiofrequency treatment were excluded.

All procedures were performed under operating room condition according to routine clinical application of our clinic. In our RFT and PRF application for TN clinic blood pressure, pulse rate, and arterial oxygen saturation of the patients are monitored continuously after intravenous access was established. Nasal oxygen is administered to the patients during the procedure. Patients is placed in supine position with their heads slightly extended. The C-arm scope is angled to the ipsilateral oblique and caudal to view the medial foramen ovale of the mandibular ramus and a submental image is obtained. The needle entry point is determined as 2.5-3 cm lateral to the labial commissure. After disinfecting the insertion site, local anesthesia is applied with 2% prilocaine. A radiofrequency needle of 10 cm with a 22-gauge, 5-mm active tip is guided into the foramen ovale with tunnel visualization. After the needle is inserted into Meckel's cave, the C-arm scope is rotated laterally to determine the depth of penetration. The tip of the electrode is appropriately placed in the Gasserian ganglion (Figure 1). Electrical stimulation is applied at 50 Hz to determine the sensory threshold and at 2 Hz to determine the motor threshold. The final position of the needle is determined as the site of paresthesia in the pain area with 0.1 to 0.3 V and muscle contraction in the mandible with 0.1-1.5 V. After a negative aspiration test, the following procedures are performed sequentially on the Gasserian ganglion: PRF (42°C, 45 V, 20 ms, 120 s), RFT (65°C, 60 s), RFT (70°C, 60 s), PRF (42°C, 45 V, 20 ms, 120 s). 1 mg/kg propofol injection is used for sedation during RFT procedures.

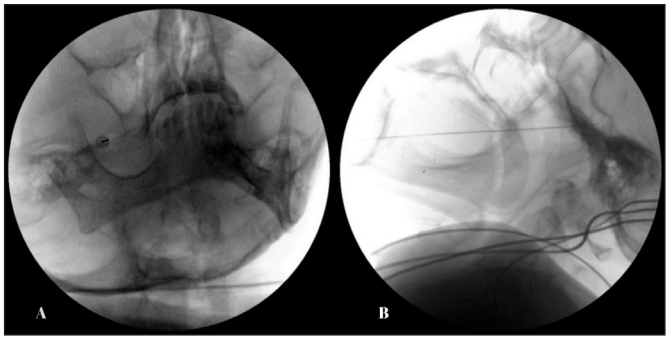

Figure 1. Placement of the radiofrequency needle in oblique submental (A) and lateral (B) cranial radiograph images.

Age, gender, painful side, duration of pain, affected branch, and visual analogue scale (VAS) and Barrow Neurological Institute Pain Intensity Scale (BNI) scores before and after (1st month, 6th month, and 12th month) the procedure were recorded.[13] Pain intensity was measured using the VAS (from 0: no pain, to 10: unbearably severe pain). The BNI score was used to evaluate the efficacy of treatment (Table 1). At 12th month after the procedure, a BNI score of 1 to 3 was considered to reflect effective treatment while a BNI score of 4 or 5 signified unsuccessful treatment. The primary outcome was defined as the effectiveness of treatment after 12 months. The secondary outcomes were VAS scores at the 1st, 6th, and 12th months after the procedure; BNI scores at the 1st and 6th months; and complications.

Table 1. Barrow neurological institute (BNI) pain intensity scale

1	No pain, no medical treatment
2	Occasional pain, no need for medical treatment
3a	No pain, continuing medical treatment
3b	Pain controlled with medical treatment
4	Partial pain, no adequate pain control with medical treatment
5	Severe pain, no pain control

Statistical Analysis

All analyses were performed using IBM SPSS Statistics 25.0 for Windows (IBM Corp., Armonk, NY, USA). Normality analysis was assessed using the Shapiro-Wilk test. Normally distributed quantitative data such as age were represented as mean±standard deviation and non-normally distributed quantitative data such as VAS scores were represented as median (minimum-maximum). Comparisons of numerical data between two dependent measurements were evaluated using the Wilcoxon signed-rank test. For variables that did not show normal distribution, the Friedman test was applied for more than two repeated measurements. Binary logistic regression analysis was used to determine factors

associated with the change in BNI pain intensity scale scores. P<0.05 was accepted statistically significant.

RESULTS

The demographic and clinical characteristics of the patients with TN are summarized in Table 2. Two-thirds of the patients were female. The mean age of the patients was 62.93±10.82 years and mean pain duration was 7.02±5.02 years. Right-sided TN was present in two-thirds of the patients. The most commonly affected branch was V3. V2 was affected in 25.9% (n=7) of the cases, V3 in 44.4% (n=12), and V2+V3 in 29.6% (n=8). There was no systemic disease in 22.2% of cases. Hypertension (59.3%) and multiple sclerosis (25.9%) were the most common associated systemic diseases. The combination of carbamazepine and pregabalin (48.1%) and carbamazepine alone (37%) were the most commonly prescribed medical treatments.

Table 2. Demographic and clinical characteristics of the patients

	Mean±SD or n (%)
Age, years, mean±SD	62.93±10.82
Gender, n (%)	
Female	18 (66.7)
Male	9 (33.3)
Duration of pain, years, mean±SD	7.02±5.02
Painful side, n (%)	
Right	18 (66.7)
Left	9 (33.3)
Affected branch, n (%)	
V2	7 (25.9)
V3	12 (44.4)
V2+V3	8 (29.6)
Systemic diseases, n (%)*	
None	6 (22.2)
Hypertension	16 (59.3)
Diabetes	3 (11.1)
Multiple sclerosis	7 (25.9)
Coronary artery disease	3 (11.1)
Congestive heart failure	1 (3.8)
Hyperlipidemia	1 (3.8)
Cerebrovascular disease	1 (3.8)
Buerger's disease	1 (3.8)
Rectal cancer	1 (3.8)
Drugs used, n (%)	
Carbamazepine	10 (37.0)
Carbamazepine and baclofen	2 (7.4)
Carbamazepine and gabapentin	2 (7.4)
Carbamazepine and pregabalin	13 (48.1)

*: Numbers indicate the total number of diseases; SD: standard deviation

VAS scores are presented in Table 3. The median VAS scores were 9.0 (8.0-10.0) before the intervention, 2.0 (0.0-9.0) at the 1st month, 2.0 (0.0-9.0) at the 6th month, and 3.0 (0.0-9.0) at the 12th month. VAS scores were significantly lower than those at baseline at all post-treatment assessment times (1st month, 6th month, 12th month) during the 12-month follow-up period (p<0.001). There was a significant change in VAS scores over time (p<0.001). Significant differences were found between the baseline VAS score and the VAS score at the 1st month and between the VAS scores at the 6th and 12th months (p<0.001), but not between the VAS scores at the 1st and 6th months (p=0.286).

The BNI pain intensity scores of the patients are shown in Table 4. BNI scores were 1-3 in 26 patients at the 1st month, 25 patients at the 6th month, and 20 patients in the 12th month after treatment. Treatment success was 96.2%, 92.5%, and 74% at the 1st, 6th, and 12th months, respectively. At the 12th month, 4 (14.8%) patients had a BNI score of 1, 6 patients (22.2%) had a BNI score of 2, and 10 patients (37%) had a BNI score of 3 [5 (18.5%) BNI 3a, 5 (18.5%) BNI 3b]. Pain control was not achieved (BNI of 4 or 5) in 7 (25.9%) of the patients. Binary logistic regression analysis revealed no association between improvement in BNI as reflected by a decrease in pain intensity from 4-5 to 1-2-3 and variables such as age, gender, duration of pain, side of TN, affected branch, or pre-procedural VAS score (p>0.05).

Table 4. BNI scores of patients over time

	1st month	6th month	12th month
BNI score (%)			
1	6 (22.2)	5 (18.5)	4 (14.8)
2	7 (25.9)	7 (25.9)	6 (22.2)
3A	9 (33.3)	10 (37.0)	5 (18.5)
3B	4 (14.8)	3 (11.1)	5 (18.5)
4	1 (3.7)	2 (7.4)	6 (22.2)
5	-	-	1 (3.7)

BNI: Barrow Neurological Institute Pain Intensity Scale

After the treatment, the dose of medication was reduced in 74.1% (20/27) patients. Complications (transient abducens paralysis in one patient and transient perioral numbness in one patient) were observed in 7.4% (2/27) of the patients, and no other significant complications or side effects were found.

Table 3. VAS scores of the patients over time

	Median (min-max)							
	Baseline	pa	1st month	pa	6th month	pa	12th month	pb
VAS	9.0 (8.0-10.0)	<0.001	2.0 (0.0-9.0)	0.286	2.0 (0.0-9.0)	<0.01	3.0 (0.0-9.0)	<0.001

VAS: Visual analogue scale, pa: Wilcoxon signed-rank test, pb: Friedman test

DISCUSSION

Pain management is challenging in patients with TN. For patients who do not respond to medications or tolerate, RFT to the Gasserian ganglion is one of the most widely accepted and frequently performed interventional procedures. Low morbidity rates and no mortality are the major advantages of RFT compared to surgical methods.[15,16] With RFT of 65°-80° applied to the Gasserian ganglion, small heat-sensitive nerve fibers (A-δ and C-type fibers) that transmit pain sensations are thermocoagulated and denatured, preventing action potential generation and providing analgesia.[10,17] Although there is no difference in pain-free periods with RFT applied at low (<75°C) and high (>80°C) temperatures, more side effects have been reported with RFT applied at high temperatures.[18,19] When the literature was examined, it was observed that RFT treatment was effective in approximately 70% to 90% of cases in the treatment of TN at 1 year after the procedure.[15,16,20] Although RFT is effective in the treatment of TN, it causes many serious complications, including facial numbness, difficulty in chewing, and decreased corneal sensation has led to consideration of PRF as an alternative to RFT. PRF provides analgesia through neuromodulation without thermal lesions of the nerve.[21,22] Studies have shown that the effects of PRF can occur at microscopic and subcellular levels, with C fibers being affected more than A-β or A-δ fibers.[23,24] Conflicting results have been reported with PRF in the treatment of TN. Some studies have reported positive effects of PRF without neurological side effects or complications.[11,25] However, Erdine et al.[26] showed that PRF was not as effective as RFT, with the short-term success achieved for only 10% of patients with TN in a randomized controlled trial.

Recently, studies have been published reporting that PRF combined with low-temperature RFT (<65°C) in the treatment of TN improves the efficacy of the treatment without significantly increasing the complications. In a randomized controlled trial, Elawamy et al.[14] applied PRF to 11 patients at 42°C, RFT to 12 patients at 75°C, and PRF at 42°C followed by RFT at 60°C to 20 patients. They observed the best results (pain-free status at 12 months) in the PRF+RFT group (70%), followed by the RFT group (50%), while pain-free status was achieved by 0% of the patients in the PRF group. The highest number of complications was observed in the RFT group among 45.4% patients, followed by the PRF group with 25% and the PRF+RFT group with 20%. The most commonly noted complications were numbness and weakness at 18.2% in the RFT group, followed by paresthesia at 10% in the PRF+RFT group. Ali Eissa et al.[27] reported the efficacy of RFT at 60-65°C together with PRF applied for 21 patients to be 66.7% at 1 year after the procedure. Ding et al.[28] compared RFT at 68°C with RFT+PRF in 40 patients and found that treatment was more effective in the RFT+PRF group than the RFT group over the course of 2 years (97.5% vs. 85%). They also reported fewer side effects and faster recovery times in the RFT+PRF group. Arıcı et al.[12] applied RFT (65°C) + PRF (42°C) for 12 patients. While there was a significant reduction in pain for 10 patients (83.3%) at the 1st month after the procedure, similar efficacy was observed for 8 patients (66.6%) at the 6th month, 5 patients (41.6%) at the 12th month, and 2 patients (16.6%) at the 24th month. Abdel-Rahman et al.[29] compared the effect of adding PRF to RFT (60°C) with the effect of RFT alone (70°C) in the treatment of recurrent TN after microvascular decompression. Treatment efficacy was similar between the groups for 2 years, but the complication rate in the RFT+PRF group was statistically lower than that in the RFT-alone group (5.61% vs. 36.8%).

In the literature, there are reports on different applications regarding the type, duration, and RFT temperature in combined PRF+RFT treatment and their superiority over each other is not yet clear. In our study, unlike previous studies, we applied 2 consecutive rounds of 60 s each of RFT at 65°C and 70°C and 120 s each of PRF at 42°C before and afterwards. We did not exceed 70°C in the RFT applications due to the increased complication rates of RFT applied at high temperatures. In our study, we were able to achieve pain reduction for 96.2% of all patients in the 1st month (BNI 1-2: 48.1%; BNI 3: 48.1%), 92.5% in the 6th month (BNI 1-2: 44.4%; BNI 3: 48.1%), and 74% in the 12th month (BNI 1-2: 37%; BNI 3: 37%). Four patients (14.8%) were completely pain-free at the 12th month. The post-procedural pain scores of our patients were significantly lower at the 1st month, 6th month, and 12th month compared to preprocedural scores, which indicates that the effect of the procedure starts early and continues for 1 year. Our success rate at the 12th month is similar to that of Ali Eissa et al.[27] The reason for our higher success rate compared to that of Arıcı et al.[12] (41.6%) may be that they performed RFT at 65°C, which is relatively low compared to our procedure, and they performed PRF for a shorter time (120 s). Ding et al.[28] reported a high success rate of 97.5% in comparison to the literature. This may be because they performed PRF for 10 min. Although Elawamy et al.[14] and Abdel-Rahman et al.[29] performed PRF for 10 min, they performed RFT at a lower temperature (60°C) than Ding et al. (68°C), which may explain their lower success rate.

More recently, the reasons for the low efficacy of PRF in the treatment of cases of chronic pain, including TN, have been investigated. In a study of rats, Tanaka et al.[30]

showed more anti-allodynic effects in the group treated with PRF for 6 min than in the groups treated with PRF for 2 or 4 min. Similarly, Chua et al.[25] claimed that PRF treatment with a pulse width of 20 ms and frequency of 2 Hz for 2 min was insufficient for TN. These data may indicate that short-term PRF treatment is insufficient for good neuromodulatory effects on the Gasserian ganglion. Currently, there is no consensus on the treatment duration, temperature, or voltage parameters for PRF combined with RFT. Different applications and success criteria may explain the significant differences in efficacy reported in various studies. The most important reason for using BNI scores as the primary outcome in our study is that, unlike VAS scores, the BNI assesses both pain and medication use at the same time. For patients who do not respond to medical treatment before radiofrequency treatment, pain may decrease with medical treatment after radiofrequency treatment and these patients should be considered to have benefited from radiofrequency treatment.

Zhao et al.[31] claimed that combining RFT with PRF reduced complications such as facial numbness, masseter muscle weakness, and decreased corneal reflex. Arıcı et al.[12] reported numbness of the tongue lasting for 1 year in only one of 12 patients who underwent PRF+RFT. In our study, postoperative complications were seen in only two patients. Anesthesia dolorosa, infection, and permanent cranial nerve palsy were not observed in any of our patients. Only one patient experienced transient abducens paralysis and one patient had transient perioral numbness.

This study had certain limitations. First, it is a retrospective study. Second, the number of patients is relatively small and no control group was included. Finally, absence of a neuropathic pain scale records and functional outcome score are other limitations.

CONCLUSION

Combined PRF+RFT treatment (2 consecutive rounds of 65°C and 70°C RFT for 60 s each and 42°C PRF for 120 s each before and after) provides significant pain relief and reduction in using analgesic drugs in patients with TN for at least 12 months without any serious complications..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 19.10.2022, Decision No: E1-22-2967).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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The severity of COVID-19 infection in children with leukemia

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ABSTRACT

Aims: The coronavirus disease 2019 (COVID-19) has been the cause of a global health crisis since the end of 2019. The aim of this study was to evaluate the clinical findings and treatment results of COVID-19 disease in pediatric patients with leukemia.

Methods: All the children and adolescents with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive real-time polymerase chain reaction (PCR) and the presence of underlying leukemia were included in the study.

Results: A total of 44 leukemia patients with COVID-19 infection were included in the study. Their primary diseases were as follows: 36 patients were newly diagnosed with acute lymphoblastic leukemia (ALL), four patients were relapsed ALL, two patients were refractory ALL, and two patients were acute myeloblastic leukemia. The mean age of patients was 104± 62 months. COVID-19 was asymptomatic in 11.4% of patients, mild in 84%, and moderate in 4.5% whereas none of our patients had a severe infection. No severe complications and/or death were observed in our study group.

Conclusion: It has been found that the clinical course of COVID-19 is mild in children and adolescents with leukemia and undergoing chemotherapy or immunosuppressive therapy.

Keywords: Children, COVID-19, leukemia

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has rapidly evolved from an epidemic outbreak in Wuhan, China.[1] As there were more than 2 million cases of COVID-19 worldwide, the World Health Organization declared COVID-19 a pandemic in March 11, 2020.[2] The SARS-CoV-2 viruses are positive single-stranded RNA viruses and primarily manifested as a respiratory tract infection. It may be cause systemic disease including cardiovascular, respiratory, gastrointestinal, neurologic, hematopoietic and immune system.[3] COVID-19 affects all age groups; however, the pediatric population accounts for only 3%-5% of total cases.[4] In children, most cases of COVID-19 are asymptomatic, and studies have revealed that children have less severe symptoms compared to adults.[5] However, some patients develop life-threatening complications such as acute respiratory distress syndrome, thrombosis, and multiorgan failure.[6]

Children with malignancy are frequently immunocompromised due to both disease itself and chemotherapy they receive which put them at high risk for severe infections, the major cause of mortality. Although data on pediatric cancer patients are limited, the mortality rate in pediatric cancer patients with COVID-19 is extremely low.[7]

This study, which was designed as a single-center retrospective observational study, was aimed to evaluate the clinical findings and treatment results of COVID-19 disease in pediatric patients with leukemia.

METHODS

The study was carried out with the permission of the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 18.01.2023, Decision No: E2-22-3196). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. An informed written consent form was not obtained due to the retrospective nature of the study.

A single-center retrospective study was conducted in our hospital. All the children and adolescents (aged 0-18 years) attending pediatric hematology with a diagnosis of leukemia with confirmed COVID-19

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from nasopharyngeal swab between March 2020 to March 2022 were included. Clinical data, demographic characteristics, and laboratory-imaging findings were retrieved from electronic medical files. COVID-19 diagnosis was obtained with real-time reverse transcription polymerase chain reaction (RT-PCR) assay (nasopharyngeal swab) for SARS-CoV-2. As our clinic policy nasopharyngeal RT-PCR test was performed in all patients and caregivers with symptoms of respiratory infection or asymptomatic patients and caregivers before hospitalization. Follow-up RT-PCR test data were collected if available. If a patient had RT-PCR positivity after a negative report with minimum 14-days period was accepted re-infection. RT-PCR tests were performed in the Microbiology Department of our hospital. Turnaround time for the COVID-19 RT-PCR test result was 6-12 hours. Data were recorded from the patient files regarding age, sex, type of leukemia, phase of treatment, symptoms, severity of COVID-19, need for hospitalization, treatment interruptions, hospital course, and outcomes. Severity of COVID-19 are described;[8]

Asymptomatic: Patients with no signs or symptoms of COVID-19.

Mild infection: Patients with mild symptoms including fever, gastrointestinal symptoms, and upper respiratory tract infection symptoms.

Moderate infection: Patients with hypoxia at rest (oxygen saturation < 93%) or presence of pneumonia. Patients with no need for intensive care unit admission.

Severe infection: Patients requiring intensive care unit admission for pneumonia or any of the following: 1. Respiratory rate >30 breaths/min (by age; 3-12 months >40, 1-3 years >30, 3-12 years >25, >12 years >20 breaths/min); 2. PaO_2/FiO_2 < 300; 3. Lung involvement > 50% on imaging within 24-48 h 4. Mechanical ventilation, septic shock, or multiorgan dysfunction.

Febrile neutropenia was defined in individuals with hematological malignancies who showed an absolute neutrophil count of less than 500/mm³ or between 500-1000/mm³ and an expected neutrophil to decrease below 500/mm³ within 24-48 h, and who had a fever as a single temperature of ≥38.3°C or >38.0°C sustained over an hour.[9] COVID-19 recovery was defined by the disappearance of the clinical symptoms in symptomatic patients. The patient was discharged when the clinical symptom improved, and the control RT-PCR result was negative.

Statistical Analysis

Statistical analyses were performed using the SPSS 15.0 statistical package programme. Descriptive statistics of the numerical parametric data were calculated as mean±standard deviation. Categorical variables were described as frequency rates and percentages.

RESULTS

The data of 139 pediatric patients with a diagnosis of acute leukemia who were assessed for SARS-CoV-2 by RT-PCR between March 2020 and March 2022 were evaluated retrospectively. The diagnosis of 117 patients was acute lymphoblastic leukemia (ALL) and 22 was acute myeloblastic leukemia (AML). A total of 44 leukemia patients with COVID-19 infection were included in the study. 36 patients were newly diagnosed ALL, four patients were relapsed ALL, two patients were refractory ALL, two patients were AML. Bone marrow transplantation was done in three of these patients due to high-risk ALL, and these patients had COVID-19 infection while receiving immunosuppressive therapy after transplantation. COVID-19 infection developed during induction, consolidation, or re-induction therapy in 16 of our patients with acute lymphoblastic leukemia and during maintenance therapy in 17 patients. The mean age of patients was 104±62 months; 57% were males, 42% were females. The characteristic features of the patients are described in Table 1.

Table 1. Characteristics and laboratory details of the patients

Patient characteristics	n	%
Age (month)	104±62	
Sex		
Male	25	57
Female	19	43
Underlying diagnosis		
Pre-B ALL	36	83
Relapsed ALL	4	9
Refractory ALL	2	4
AML	2	4
Haemoglobin, g/dL	9.1 (7-11.5)	
White blood cells (/mm³)	1900 (400- 3800)	
Neutrophil count (/mm³)	700 (100-1600)	
Lymphocyte count(/mm³)	980 (550- 1800)	
Platelet count (/mm³)	84000 (11000- 183000)	
CRP (mg/L)	68 (10-195)	

The most common symptoms were fever (n=20, 45.4%), cough (n=15, 34%), sore throat (n=4, 9%), nasal congestion (n=3, 6%), respectively. Mean duration of febrile days was 2.5±2.4 days. The COVID-19 RT-PCR test was positive at the time of initial diagnosis in four patients, and these patients presented with fever. These patients were admitted to our infection service with a diagnosis of ALL and, steroid treatment was started in accordance with the chemotherapy protocol, and intrathecal treatment was performed within the first 3 days. In ALL patients, 6 patients were receiving

induction therapy, 6 were receiving consolidation therapy, 4 were receiving re-induction therapy, 17 were receiving maintenance therapy, 4 were receiving relapsed therapy, 2 were receiving salvage therapy, and 1 patient was in pre-transplantation period and 2 patients were in the post-transplant period. Two patients were receiving AML protocol.

Neutropenia was present in 54.5% of our patient. The mean neutrophil count of our neutropenic patients was 520± 415/mm³. None of the patients had a positive blood or catheter culture. The treatment of patients who received active chemotherapy were interrupted until the SARS-CoV-2 RT-PCR result was negative. The mean days for PCR negativity was 12.3±8.1 days. One of our patients became negative on the 45th day and chemotherapy of this patient was started when the COVID-19 cycle threshold value (the number of cycles that the fluorescent signals undergo to reach the threshold and < 25 values indicate high viral load and >25 indicate low viral load) was 27 on the 39th day of COVID-19 RT-PCR positivity.

According to the disease severity score, 5 patients (11.4%) were asymptomatic, 37 patients (84%) had mild infection, and 2 patients (4.5%) had moderate infection whereas none of our patients had severe infection. One ALL patient receiving maintenance treatment and one with refractory disease developed moderate infection. The patient who was on maintenance therapy, had bilateral air bronchograms and patchy consolidations in her thorax computed tomography, consistent with COVID-19 pneumonia (**Figure 1**) and corticosteroid treatment was given with antibiotics. After 4 weeks of hospitalization, this patient was discharged and continued maintenance therapy. In two patients, COVID-19 RT-PCR positivity was detected again approximately two months after their test became negative and the chemotherapy of these patients were interrupted again.

None of the patients developed multisystem inflammatory syndrome during follow-up. No severe complications and/or death were observed in our study group.

DISCUSSION

In the past two years, it has been clearly demonstrated that critical disease due to COVID-19 is rare in children and the disease progresses milder in children compared with adults.[10] Although few data are available regarding the effect of COVID-19 on pediatric patients with leukemia, the rate of the asymptomatic disease has been reported between 30-80%.[11,12] Among patients with all types of malignancy and COVID-19, children also experience less morbidity and mortality than adults. Only 4-9% of pediatric oncology patients experience a severe or critical COVID-19 course compared to 55% of adult oncology patients.[13,14] Furthermore, the mortality rate of COVID-19-positive pediatric oncology patients was 4%, however mortality rate was 28% in adults with cancer and COVID-19.[15-17]

In this study, 58% of the patients were male, which was consistent with the other studies that reported no significant differences between gender in pediatric patients.[18]

The most common presenting symptom of our patients with COVID-19 were fever as the patients that reported in the most international studies.[19,20] Most pediatric cancer patients with COVID-19 were noted to have a relatively mild illness and it has been claimed that hospitalized cancer patients with COVID-19 were often admitted because of problems with their primary diseases rather than complications of COVID-19 infection.[11,12] Similarly, most of our patients had mild infection, whereas only two patients had moderate infection. Although febrile neutropenia was thought to be a risk factor for a severe COVID-19 infection, we could not observe this in our patients.[21] In the Global COVID-19 in Childhood Cancer Registry, a severe disease frequency was found as 18.4% and death was reported in 3.4% of children with malignancy.[22] In our cohort, none of our patients were followed up in the intensive care unit and no death was observed. Further, none of our patients developed any of the chronic complications of COVID-19, including multisystem inflammatory syndrome in children, after recovering

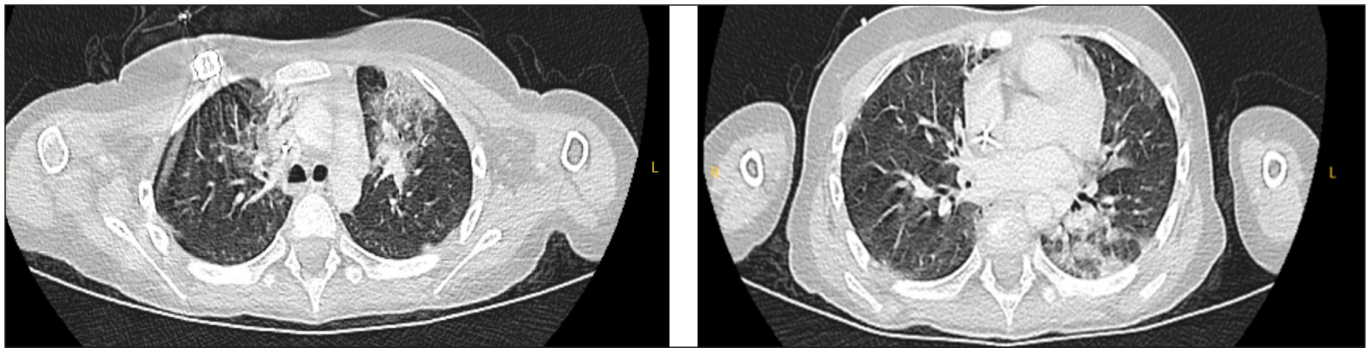

Figure 1a,1b. A computed tomographic scan of the chest showing bilateral air bronchograms and patchy consolidation

from the infection. MIS-C is a heterogeneous manifestations of systemic inflammation and shock and increasingly reported among children and adolescents who already developed antibody against COVID-19.[23] In previous studies, the rates of hospitalization in intensive care, respiratory support and mortality were found to be 63-80%, 33-56% and 0.8-3%, respectively, in healthy children who developed MISC.[24] Our results may be explained by the role of chemotherapy-related immune suppression in the protection against the development of cytokine release storm.[25]

In our study, none of the patients had positive blood cultures. Sepulveda et al.[26] reported that bloodstream infections are very rare in adult and non-malignant patients with COVID-19, like our findings but there are no studies available in pediatric patients.

Chemotherapy was withheld even in asymptomatic patients for all COVID-19 positive patients. So far, no increase in malignancy-related morbidity, relapse or mortality due to this delay of chemotherapy has been noticed.

This study has some limitations. First, it was a retrospective study, and our cohort included a small number of patients. It may be difficult to interpret the data and come to a definite conclusion with a such limited patient group, but all novel information about COVID-19 in special patient groups is valuable for researchers. More prospective studies with larger sample sizes are needed in this subject to elucidate the long-term follow-up results in pediatric patients with leukemia.

CONCLUSION

It has been found that the clinical course of COVID-19 is mild in children and adolescents with leukemia and undergoing chemotherapy or immunosuppressive therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 18.01.2023, Decision No: E2-22-3196).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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The clinical course of COVID-19 in pregnant and non-pregnant women

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ABSTRACT

Aims: Pregnancy is a physiological condition that predisposes women to respiratory complications of viral infections thus, bringing the risk of developing more severe disease. The aim of this research was to elucidate the clinical course of COVID-19 in pregnant and non-pregnant women of childbearing age. Mortality rate, laboratory parameters, the occurence of cytokine storm in both groups and the response to treatment have been investigated.

Methods: A total of 88 women of childbearing age with a diagnosis of COVID-19 disease has been retrospectively analyzed. Age, comorbidity, length of stay in the intensive care unit and treatment regimen of patients have been obtained from hospital database. Ferritin, IL-6, CRP, procalcitonin, D-dimer, urea, creatinine, GFR, ALT, AST, LDH, lymphocyte count, neutrophil count, white blood cell count were evaluated. Clinical response such as reduction in oxygen requirement and vasopressor utilization before and after treatment were examined

Results: The rate of RT - PCR positive results were statistical significantly higher in pregnant women (p=0.003). The median WBC, lymphocyte and leukocyte values of the pregnant patients were higher (p=0.038, p=0.006 and p=0.035, respectively). The median hemoglobin, LDH and ferritin values of pregnant women were lower than those of non-pregnant individuals (p=0.032, p<0.001 and p=0.010, respectively). Mortality has been observed wit a rate of 17.5% in second trimester and 15% in the third trimester while 22.5% of women in the second trimester and 45% of women in the third trimester have survived COVID-19 infection.

Conclusion: Regarding the results of this study, we have observed differences in WBC, lymphocyte and leukocyte, median hemoglobin, LDH and ferritin values of pregnant women and non-pregnant individuals. Additionally, mortality rate was also comparable.

Keywords: COVID-19, pregnancy, mortality, D-dimer

INTRODUCTION

The novel Coronavirus disease (COVID-19), also called SARS-CoV-2, emerged as an urgent global public health problem, has rapidly spread to the rest of China and beyond into a pandemic after it was first reported in Wuhan, Hubei Province, China in December 2019.[1,2] In parallel with this, researches on COVID-19 have increased in every field and took their place in the literature.[3,4] The critical point in the management of any infectious disease is the care of the vulnerable population. It is known that pregnant women are disproportionately affected by respiratory diseases associated with increased infectious morbidity and maternal mortality rate.[5,6] According to the report by World Health Organization (WHO) on March 3, the predicted global mortality rate was 3.4% for COVID-19 infection.[7]

Pregnancy is a physiological condition that predisposes women to respiratory complications of viral infections. Infection of pregnant women with respiratory viruses due to physiological changes in the immune and cardio-pulmonary systems brings the risk of developing more severe disease. Virus infections are known to be responsible for serious complications during pregnancy, including endotracheal intubation, hospitalization in the intensive care unit (ICU), renal failure, and death.[5,6] The case fatality rate due to SARS-CoV infection in pregnant women is approximately 25%.[5] There is no evidence that COVID-19 causes intrauterine infection and creates a congenital infection, but it is difficult to make a definite decision due to the low number of cases.

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One of the largest series on COVID-19 in pregnancy is the study that included 215 pregnant patients during the New York pandemic attack.[8] SARS-CoV-2 positivity was detected at a rate of 15% in the screening performed in pregnant women (n=33) and it was stated that the majority of these patients were asymptomatic. Accordingly, it was reported that 13.5% of asymptomatic patients were found to be positive for SARS-CoV-2. In another study, it was observed that symptoms developed during labor or in the postpartum period in 71% of cases that were asymptomatic at presentation.[9]

United States Centers for Disease Control and Prevention, it was reported that the rate of asymptomatic cases in pregnant and non-pregnant patients was similar. Accordingly, 97.1% of pregnant women and 96.9% of non-pregnant women were symptomatic. In addition, the frequency of symptoms in pregnant and non-pregnant patients was similar.[10]

Pregnancy and birth in general, does not increase the risk of SARS-CoV-2 transmission and does not worsen the clinical course of COVID-19 disease compared to women of similar age who are not pregnant.[8,9] In most of the cases (>90%), mothers recover without the need for delivery.[11-15] However, considering age, underlying diseases and ethnicity in pregnant women, the rates of intensive care admissions were higher (1.5% vs. 0.9%; RR 1.5, 95% CI 1.2-1.8) and it was reported that the requirement for mechanical ventilation was more frequent (0.5% vs. 0.3%; RR 1.7, 95% CI 1.2-2.4) but mortality rates did not change.[10]

Again, in a study conducted in the United States, it was shown that 27% of pregnant women with COVID-19 were mild, 26% were seriously ill and 5% were critically ill.[16] In addition, serious disease is more common in late pregnancy.[17]

The frequency of preterm birth and cesarean section increases in cases with COVID-19 during pregnancy. Fever and hypoxemia may increase preterm labor due to premature rupture of membranes and abnormal fetal heart rate patterns. However, preterm birth can be seen in patients without serious respiratory disease. In a systematic review examining 790 cases who had COVID-19 during pregnancy, the delivery rate before 37 weeks was reported as 23% (OR: 2.28, 95% CI 0.92-5.65) and the cesarean rate was 72%.[18] In a study conducted in the United Kingdom involving 427 pregnant COVID-19 patients, the rate of preterm delivery was reported as 27% and the rate of cesarean section as 59%.[19] However, most of the preterm deliveries were iatrogenic rather than spontaneous.[20]

Although data on the first trimester are limited, the risk of spontaneous abortion does not seem to increase in pregnant women with COVID-19.[15,21]

The aim of this research was to elucidate the clinical course of COVID-19 in pregnant and non-pregnant women of childbearing age. Mortality rate, laboratory parameters, the occurence of cytokine storm in both groups and the response to treatment have been investigated.

METHODS

The study was carried out with the permission of the Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 12/01/2022, Decision No: E1-22-2293). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was designed as a single-center and retrospective study. Patients over the age of 18 years, who have been admitted to our institution between 01.03.2020 and 01.03.2022 with a confirmed reverse transcription -polymerase chain reaction (RT - PCR) result and radiologic findings have been included in this research.

Age, comorbidity, length of stay in the intensive care unit and treatment regimen of pregnant and non-pregnant female patients of childbearing with a confirmed diagnosis of COVID-19 have been obtained from hospital database.

Ferritin, interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin, D-dimer, urea, creatinine, glomerular filtration rate (GFR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), white blood cell (WBC) count, lymphocyte count, neutrophil count, and platelet count were evaluated.

Clinical response such as reduction in oxygen requirement and vasopressor utilization before and after treatment were examined. In addition, mortality rate, laboratory parameters, the occurence of cytokine storm in both groups and the response to treatment have been investigated.

Inclusion and Exclusion Criteria

Women over 18 years of age, with childbearing potential who had a confirmed diagnosis of COVID-19 via laboratory and radiologic parameters have been enrolled in this study. Women out of childbearing age, individuals who had passed 14 days after RT - PCR positivity on post-covid period have been excluded from the study.

Data Analysis and Statistics

Shapiro Wilk test was utilized for assessing whether the variables follow normal distribution or not. Continuous variables were presented as median (minimum:maximum) and mean±standard deviation values. Categorical variables were reported as n (%). According to the normality test results, Independent sample t test or Mann Whitney U test was used in comparison between two groups. Pearson Chi-square test, Fisher's exact test and Fisher Freeman Halton Test were used for comparing categorical variables. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.) was used for statistical analysis and. A p value <0.05 was considered statistically significant.

RESULTS

A total of 88 women of childbearing age with a diagnosis of COVID-19 disease has been retrospectively analyzed (Figure).

The comparison of age, RT - PCR result, computed tomography (CT), treatment and laboratory parameters have been elaborated in Table 1. When the table was examined, no statistically significant difference was found between the groups in terms of age distribution (p=0.096). There was a statistical significance between the groups according to the RT - PCR results, and it was seen that the rate of those with positive PCR results was higher in the pregnant women (p=0.003).

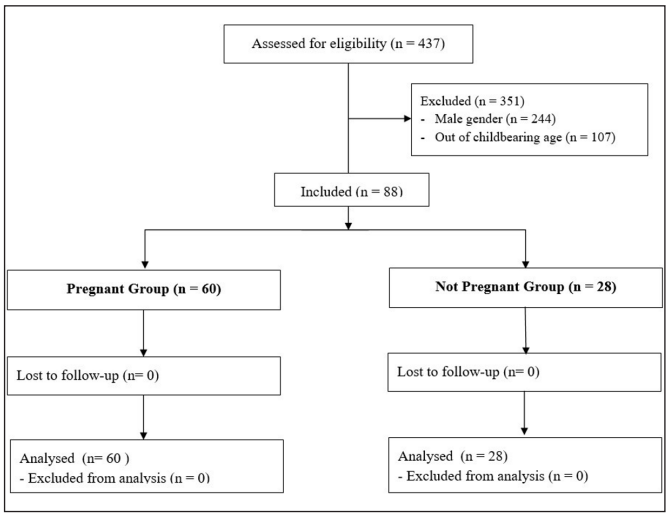

Figure. Flow chart of the patients.

Table 1: Comparison of demographic and clinical characteristics between pregnant and non-pregnant patient groups

	n	Pregnant	n	Non Pregnant	p-value
Age (years)	60	29 (23:40)	28	34.50 (20:39)	0.096[a]
RT - PCR	60		28		0.003[b]
Positive		56 (93.33%)		19 (67.86%)	
Negative		4 (6.67%)		9 (32.14%)	
CT Result	21		25		>0.99[b]
COVID-19 findings		20 (95.24%)		23 (92%)	
No COVID-19 findings		1 (4.76%)		2 (8%)	
WBC	60	9.35 (4.10:29.60)	28	6.61 (2.35:37.60)	0.038[a]
Lymphocyte	60	0.75 (0.15:4.50)	28	0.62 (0.14:1.25)	0.006[a]
Neutrophil	60	7.65 (2.79:26.30)	28	5.65 (1.94:35.60)	0.035[a]
Platelet	60	295.50 (99:720)	28	268.50 (58:478)	0.284[a]
Hemoglobin	60	11.20 (5.70:15.20)	28	11.80 (4.60:15.70)	0.032[a]
AST	60	41 (12:733)	28	43.50 (12:237)	0.893[a]
ALT	60	25.50 (5:550)	28	25 (6:310)	0.788[a]
LDH	60	383.50 (213:3821)	28	529 (314:1081)	<0.001[a]
Ferritin	60	84.50 (11:1748)	28	177 (10:1075)	0.010[a]
CRP	60	83 (0.20:198)	28	73.50 (25:218)	0.230[a]
IL - 6	60	12.50 (2:1000)	28	10 (2:1360)	0.943[a]
D - dimer	60	1.73 (0.19:31)	28	1.21 (0.29:26)	0.081[a]
H SCORE	58	2 (0:4)	28	2 (1:5)	0.989[a]
PCT	60	0.13 (0.02:3.70)	28	0.06 (0.02:36)	0.114[a]
Steroid usage	59		28		0.436[c]
dxm		2 (3.39%)		1 (3.57%)	
40 mg		8 (13.56%)		1 (3.57%)	
80 mg		7 (11.86%)		4 (14.29%)	
250 mg		24 (40.68%)		9 (32.14%)	
>250 mg		12 (20.34%)		8 (28.57%)	
yok		4 (6.78%)		5 (17.86%)	

Data are expressed as n (%) and median (minimum:maximum). a: Mann Whitney U Test, b: Fisher's Exact test, c: Fisher Freeman Halton Test, COVID-19: Coronavirus disease 2019; RT - PCR: reverse transcription - polymerase chain reaction; IL-6: interleukin-6; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; WBC: white blood cell ; CT: computed tomography; PCT: procalcitonin

It was determined that there was a statistically significant difference between the groups in terms of WBC, lymphocyte, leukocyte, hemoglobin, LDH and ferritin values. It is observed that the median WBC, lymphocyte and leukocyte values of the pregnant patients were higher (p=0.038, p=0.006, and p=0.035, respectively). The median hemoglobin, LDH and ferritin values of pregnant women were lower than those of non-pregnant individuals (p=0.032, p<0.001, and p=0.010, respectively). No statistically significant difference was found in the comparisons of other variables included in Table 1 (p>0.05).

There was no statistically significant difference between the groups in terms of treatment intervention. Entubation, Continuous Renal Replacement Therapy (CRRT), hemodiafiltration (HDF), Extracorporeal membrane oxygenation (ECMO), non - invasive mechanical ventilation (NIMV), vasopressor inotropic usage variables did not differ between the groups (Table 2) (p>0.05). Since the number of patients who underwent mechanical ventilation (MV) in the study groups was insufficient for statistical comparison, no significance has been achieved. Additionally, mortality, bacterial colonisation, onset of symptoms, duration of MV and ICU stay was comparable between pregnant and non - preganant women (Table 2).

There was no statistically significant difference between the number of patients in the 2nd and 3rd trimesters, post - partum period or non - pregnant women (Table 3) (p>0.05).

Majortiy of the patients (75%) had no comorbidity, while asthma has been observed in 5.68% individuals, diabetes mellitus 2.27% and hypothyroidism in 2.27% of the enrolled subjects (Table 4).

The mortality rate of pregnant women has been denoted in Table 5. When the table was examined, mortality has been observed in 17.5% in second trimester and 15% in the third trimester while 22.5% of women in the second trimester and 45% of women in the third trimester have survived COVID-19 infection.

Table 3. Pregnancy status of study population

	n=88
2nd trimester	16 (18.18%)
3rd trimesters	24 (27.27%)
Post-partum	20 (22.73%)
Non Pregnant	28 (31.82%)

Data are expressed as n(%).

Table 2. Interventions applied to treatment groups

	n	Pregnant	n	Non Pregnant	p value
Entubation	60		28		0.134[d]
No		20 (33.33%)		5 (17.86%)	
Yes		40 (66.67%)		23 (82.14%)	
NHFO	60		28		0.732[d]
No		49 (81.67%)		22 (78.57%)	
Yes		11 (18.33%)		6 (21.43%)	
NIMV Requirement	59		28		>0.99[b]
No		4 (6.78%)		2 (7.14%)	
Yes		55 (93.22%)		26 (92.86%)	
Vasopressor inotropic usage	60		28		0.414[d]
No		13 (21.67%)		4 (14.29%)	
Yes		47 (78.33%)		24 (85.71%)	
HDF	60		28		0.318[b]
No		0		1 (3.57%)	
Yes		60 (100%)		27 (96.43%)	
CRRT	60		28		0.538[b]
No		1 (1.67%)		1 (3.57%)	
Yes		59 (98.33%)		27 (96.43%)	
ECMO	60		28		0.173[b]
No		5 (8.33%)		0	
Yes		55 (91.67%)		28 (100%)	
Mortality	60		28		0.197[d]
Survived		44 (73.33%)		24 (85.71%)	
Deceased		16 (26.67%)		4 (14.29%)	
Bacterial Colonisation	60		28		0.478[d]
No		21 (35%)		12 (42.86%)	
Yes		39 (65%)		16 (57.14%)	
Onset of symptoms	60	5 (1:17)	28	4 (1:10)	0.101[a]
Duration of MV*	20	4.50 (1:28)	4	13.50 (4:35)	-
ICU Stay	60	6 (1:40)	28	7.5 (2:50)	0.261[a]

Data are expressed as n (%) and median (minimum:maximum). a: Mann Whitney U Test, b: Fisher's Exact test, d:Pearson Chi-Square Test, * Since the number of units was insufficient for statistical analysis, comparisons between groups could not be made. HFNO: high-flow nasal oxygen; CRRT: Continuous Renal Replacement Therapy; HDF: hemodiafiltration; ECMO: Extracorporeal membrane oxygenation; NIMV: non - invasive mechanical ventilation; MV: mechanical ventilation; ICU: intensive care unit

Table 4. Comorbid diseases of the study population

	n=88
Asthma	5 (5.68%)
Multipl Cerebral Infarct +Aortic Vegetation + HIV+	1 (1.14%)
DM	2 (2.27%)
DM (Diabetic Ketoacidosis)	1 (1.14%)
Down Syndrome	1 (1.14%)
Hypothyroidism	2 (2.27%)
Hypertension	1 (1.14%)
Hyperteinsion+CRF+Mental Retardation	1 (1.14%)
Valve Replacement	1 (1.14%)
Malignancy (Cured lymphoma)	1 (1.14%)
Obesity	1 (1.14%)
SLE	1 (1.14%)
Thalassemia Carrier	1 (1.14%)
Long QT Syndrome	1 (1.14%)
None	66 (75%)

Data are expressed as n(%). DM: diabetes mellitus; SLE: Systemic lupus erythematosus; CRF: chronic renal failure.

Table 5. Mortality, duration of MV, ICU stay and H SCORE with respect to gestational period

	n	2nd Trimester	n	3rd Trimester	p value
Mortality	16		24		0.215[d]
Survived		9 (22.50%)		18 (45%)	
Deceased		7 (17.50%)		6 (15%)	
Duration of MV	8	3 (1:24)	8	4.50 (1:19)	0.798[a]
ICU Stay	16	5.50 (1:31)	24	7 (2:28)	0.576[a]
H SCORE	16	2.31±1.40	22	2±1.07	0.440[e]

Data are expressed as n (%), median (minimum:maximum) and mean±standard deviation. a: Mann Whitney U Test, d:Pearson Chi-Square Test, e: Independent Sample t Test, ICU: intensive care unit; MV: mechanical ventilation.

DISCUSSION

Due to its physiological structure, the pregnancy period reduces the defense of women against viral infections and suppresses the immune system. It is known that pregnant women have an increased risk of morbidity and mortality in respiratory tract infections such as influenza. Therefore, pregnant women are considered to be a risky group for COVID-19.[22] In a large international systematic review, it was found that the mortality rate of pregnant women with COVID-19 was not high, but their care needs were increased.[23] In published articles it has been determined that COVID-19 causes complications such as premature rupture of membranes, preterm labor and fetal distress in pregnant women.[23,24]

It has been reported that premature rupture of membranes develops, and an emergency cesarean section was performed in one pregnant woman due to preterm labor. In a study conducted by Zhu et al.[25] in nine pregnant women with COVID-19, fetal distress was reported in six of them. In this context, pregnant women infected with COVID-19 should be followed closely by healthcare professionals in terms of possible complications.

Although it has been reported that pregnant women in the third trimester are at higher risk, it has also been reported that maternal deaths from COVID-19 are not at an alarming level.[26,27] In a study examining the effect of severe acute respiratory syndrome on pregnancy, it was reported that, diseases that cause severe respiratory symptoms may trigger fetal death, miscarriage, and congenital anomalies during early pregnancy.[28] In addition, in a study conducted in the United Kingdom, the maternal mortality rate was found to be 5.8/100.000.[19] In this study mortality has been d observed in 17.5% in second trimester and 15% in the third trimester, while 22.5% of women in the second trimester and 45% of women in the third trimester have survived COVID-19 infection.

It is recommended to perform CT and RT-PCR tests in the diagnosis of COVID-19, and it is reported that both should be performed in order to establish the definitive diagnosis in the most reliable way.[29] Ground glass opacities detected on CT are found in most patients with COVID-19 and recommended for diagnosis. Exposure of the fetus to radiation in CT is very low.[30,31] Despite this, American College of Obstetricians and Gynecologists recommends that CT should be performed by protecting the abdomen when necessary.[32] In this study there was a statistical significance between the groups according to the RT - PCR results, and it was seen that the rate of those with positive PCR results was higher in the pregnant women.

Studies have shown that increased amounts of proinflammatory cytokines in serum are associated with pulmonary inflammation and extensive lung injury. The severity of the cytokine storm may be one of the mechanisms involved in the occurrence, development and prognosis of COVID-19. Complete blood count, IL-6, D-dimer and other laboratory parameters can be stated as an important predictor of inflammatory progression both in the diagnosis of COVID-19 and in intensive care hospitalization.[33] In studies with COVID-19 it was observed that while mild WBC increase was observed in patients with severe disease symptoms, there was a significant increase in patients who were deceased. The increase in leukocyte levels can be counted as a parameter that shows the deterioration of the clinic. In addition to leukocytosis, an increase in neutrophils and a decrease in lymphocytes, monocytes and eosinophils were found in various studies.[34] In this study we have observed that the median WBC, lymphocyte and leukocyte values of the pregnant patients were statistically higher than non-pregnan women.

Cytokin storm plays an important role in critical patient groups with SARS-CoV-2 infection which is mainly characterized by elevated plasma IL-6 levels.[33] According to recent COVID-19 studies it was elaborated that the level of IL-6 in the severe group was higher than that in the moderate group, suggesting that IL-6 can be used as a biomarker for severity assessment.[35] However, the correlation of IL-6 levels in critically ill patients is still unknown. It the current study the decrease IL-6 levels after COVID-19 in the group with mortality was significantly higher compared to pre-COVID-19 levels. In this study there was no difference in the occurence of cytokine storm between pregnant and non-pregnant patients.

Ferritin, a protein that functions as an iron storage, increases as a result of the activation of macrophages and hepatocytes in COVID-19. Unlike other viral infections, ferritin shows a moderate increase in cytokine storm syndrome. It is thought that it can be used as a predictive marker in sepsis mortality. In the current study, ferritin decreased in the group with mortality while it increased

in the group without mortality.[36] In this study there was a statistically significant difference between the groups in terms of WBC, lymphocyte, leukocyte, hemoglobin, LDH and ferritin values. The median hemoglobin, LDH and ferritin values of pregnant women were lower than those of non-pregnant individuals (p=0.032, p<0.001, and p=0.010, respectively).

Hypercoagulopathy is associated with the severity of COVID-19 symptoms, and D-dimer levels are one of the main parameters to consider when evaluating coagulopathy in COVID-19 patients. As COVID-19-associated coagulopathy differs from disseminated intravascular coagulation, high D-dimer levels are strongly associated with disease severity and increased mortality, so it is necessary to closely monitor the dynamics of coagulation parameters in COVID-19 patients. In the current study D - dimer level decreased in the mortality group and increased in the group without mortality.[37]

There is no meaningful data published yet on how pregnancy is affected in the first trimester. Influenza virus has been reported to increase abortion rates.[38] In the following weeks of pregnancy, based on studies on other viral infections, complications up to perinatal mortality can be expected in the presence of COVID-19.[39] In general, cases with mild infections are also common in pregnant women. About 15% of asymptomatic cases are reported. Almost all patients undergoing radiological imaging have pneumonia findings. An increased incidence has been reported, especially in preterm birth rates. However, there is no evidence of an increased incidence of preeclampsia.[40] In this study majortiy of the patients (75%) had no comorbidity, while asthma has been observed in 5.68% individuals, diabetes mellitus 2.27% and hypothyroidism in 2.27% of the enrolled subjects.

This study has limitations. The main limitation of this study could be attributed to its retrospective nature. The relatively small sample size could be another limitation.

CONCLUSION

Regarding the results of this study, we have observed differences in WBC, lymphocyte and leukocyte, median hemoglobin, LDH and ferritin values of pregnant women and non-pregnant individuals. Additionally, mortality rate was also comparable.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 12/01/2022, Decision No: E1-22-2293).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Optimized machine learning based predictive diagnosis approach for diabetes mellitus

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ABSTRACT

Aims: Diabetes mellitus is a metabolic disease caused by elevated blood sugar. If this disease is not diagnosed on time, it has the potential to pose a risk to other organs and tissues. Machine learning algorithms have started to preferred day by day in the detection of this disease, as in many other diseases. This study suggests a diabetes prediction approach incorporating optimized machine learning (ML) algorithms.

Methods: The framework presented in this study starts with the application of different data pre-processing processes. Random forest (RF), support vector machine (SVM), K-nearest neighbor (K-NN) and decision tree (DT) algorithms are used for classification. Grid search is utilized for hyperparameter optimization of algorithms. Different performance evaluation measures are used to find the algorithm that best predicts diabetes. PIMA Indian dataset (PID) is chosen for testing the experiments. In addition, it is investigated to what extent the attributes in the data set affect the result using Shapley additive explanations (SHAP) analysis.

Results: As a result of the experiments, the RF algorithm achieved the highest success rate with 89.06%, 84.33%, 84.33%, 84.33% and 0.88% accuracy, precision, sensitivity, F1-score and AUC scores. As a result of the SHAP analysis, it is found that the "Insulin", "Age" and "Glucose" attributes contributed the most to the prediction model in identifying patients with diabetes.

Conclusion: The hyperparameter optimized RF approach proposed in the framework of the study provided a good result in the prediction and diagnosis of diabetes mellitus when compared with similar studies in the literature. As a result, an expert system can be designed to detect diabetes early in real time using the proposed method.

Keywords: Machine learning, diabetes mellitus, data preprocessing, grid search, random forest

INTRODUCTION

Diabetes mellitus (DM) is one of the diseases that threaten public health at significant rates. Insufficient or no insulin production in the body for any reason or insensitivity of body tissues to insulin causes diabetes.[1] Symptoms such as dry mouth, nocturia, polyuria, polydipsia, loss of appetite, blurred vision, weight loss, itching, recurrent fungal infections are frequently seen in diabetic patients.[2] DM can cause many problems in a person's health due to the effects it creates. Common problems caused by diabetes include heart diseases, vascular diseases, vision loss, kidney failure, and nervous system diseases.[3] According to published statistics, there are more than 500 million diabetics worldwide as of 2021. It is predicted that the incidence of DM will reach over 600 million in 2030 and over 700 million in 2045. In 2021, DM caused over 6.5 million deaths in 2021.[4] Therefore, early diagnosis of diabetes is essential procedure in terms of reducing the incidence of diabetes and reducing the problems that diabetes can cause.[5]

In order to diagnose diabetes in the early period, it is done by examinations by health professionals and examining blood samples taken from patients in a laboratory environment.[1] However, due to the fact that diabetes is a disease that progresses without showing many symptoms, it may not be clearly diagnosed at times. The artificial intelligence (AI), which is successfully used in the diagnosis and prediction of many diseases such as cancer, heart, skin, genetic and neurological disorders, can be used in the prediction of diabetes.[6] In addition to learning from known data, AI is a structure that includes analytical algorithms and allows computers to perform many complex operations. In addition to learning from known data, AI is a structure that includes analytical algorithms and allows computers to perform many complex operations. The working areas of AI are shown in **Figure 1**. Machine learning (ML) is a field of AI that helps a computer learn with the data it uses, increases the

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performance of systems, and uses mathematical models for these operations. These algorithms are critical for building a data model that predicts future states from known data. ML can be grouped supervised learning algorithms such as classification and regression process, unsupervised learning algorithms such as cluster analysis and reinforcement learning algorithms such as decision making. Neural network is type of ML algorithm created by modeling neural networks in the brain of living things. Deep learning is a kind of machine learning algorithm model that automatically creates the hierarchy of the presented data by using multi-layered neural networks as a model.[7] ML contributes to the interpretation of health data, which is especially difficult to learn and cannot be analyzed by traditional statistical methods. While building ML algorithms, different hyperparameter sets should be tested and appropriate hyperparameters should be selected. The only way to determine them is through multiple experiments on models by selecting a set of hyperparameters. This process is called hyperparameter optimization. Choosing the right hyperparameters directly affects the performance of ML algorithms. Considering that there are tens of hyperparameters and tens of values that these hyperparameters can take for a ML algorithm, it is clear how difficult it would be to try all combinations one by one and choose the best combination. For ML algorithms, it is useful to use the hyperparameter optimization method to determine the best hyperparameters. Hyperparameter optimization is the process of finding the most appropriate hyperparameter combination according to the success metric determined for a ML algorithm.[8] Therefore, hyperparameter optimization is an extremely useful process for building a successful model.

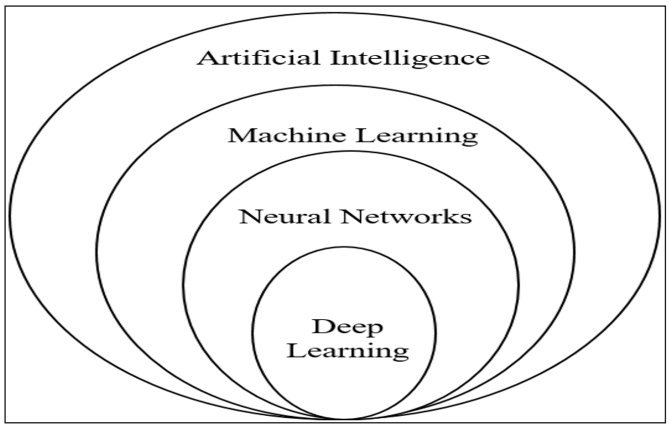

Figure 1. The working areas of AI

In this study, using a data set, an effective prediction model is proposed to determine whether a patient has diabetes with different ML algorithms. Within this scope, this study proposes an effective predictive diagnostic model for diabetes using four different supervised ML models predictive diagnosis approach for diabetes with the four ML algorithms optimized by grid search (GS) hyperparameter optimization.

The ML algorithms used in the study are as follows: Decision Tree (DT), Support Vector Machine (SVM), K-Nearest Neighbor (K-NN) and Random Forest (RF).

In this study, the diagnostic performances of ML in diabetes are compared with each other to create an effective predictive model and the most successful method is tried to be determined.

Different performances criteria are used to determine the ML method that best detects diabetes.

Shapley additive explanations (SHAP) values are utilized to show the effect of attributes on model success.

LITERATURE SURVEY

The studies related to the prediction of DM are investigated, it is seen that many classification models have been proposed by using ML algorithms. One of the most common open datasets used for the prediction DM is the dataset named "Pima Indians Diabetes" (PID). One of the studies in which this dataset was included Birjais et al.[9] has conducted. Gradient boosting (GB), logistic regression (LR), and naive Bayes (NB) classifiers were preferred to predict whether a person is diabetic. GB algorithm with 86% accuracy achieved the best result. Tigga et al.[10] preferred LR, K-NN, SVM, NB, DT and RF algorithms. The 10-fold cross validation results are 77%, 74.2%, 77%, 75.6%, 74.9% and 77.4%, respectively. Singh and Singh[11] utilized a stacked ensemble approach for prediction of DM. The proposed model achieved 83.8% of accuracy. Lyngdoh et al.[12] utilized K-NN, NB, SVM, DT and RF algorithms for prediction of DM. K-NN algorithm achieved 76% of accuracy. Kumari et al.[13] applied different ML algorithms for prediction process. Soft voting classifier (SVC) achieved of 79.08% accuracy Chang et al.[14] suggested ML-based model for prediction of DM. RF algorithm achieved 82.26% of accuracy compared to other ML algorithms. Yakut[15] utilized RF, Extra Tree Classifier and Gaussian Process Classifier for prediction of DM. RF achieved 81.71% of accuracy.

METHODS

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. An open data set was used in this study. Thus, ethics committee approval was not obtained.

The suggested methodology for diagnosing diabetes is presented in this section. The flowchart of suggested predictive model for diabetes mellitus is shown in the Figure 2. The suggested model is starting with diabetes

dataset acquisition. Then, various data pre-processing process are performed. After data pre-processing stage, ML algorithms process is starting. In the next stage, the hyperparameters of ML algorithms is automatically selected by using GS approach. Then, using performance measure metrics, the ML algorithms are compared and the best classifier is determined for prediction of diabetes. At the last stage, the effect of the features on the result of the model with the best prediction rate is determined by SHAP analysis. All the experiments were conducted using a Jupyter Notebook (6.3.0)[16] environment running Phyton (3.8.8)[17] on Windows 10. A personal computer used to run the simulation created in the study is equipped with an Intel Core i7 8750 CPU processor and 16 GB of memory. The simulation libraries are used as follows: Data pre-processing, data splitting, ML modelling, evaluation and plotting (sklearn, PyOD, Numpy, pandas, SciPy, matplotlib, skicitplot and seaborn).[18]

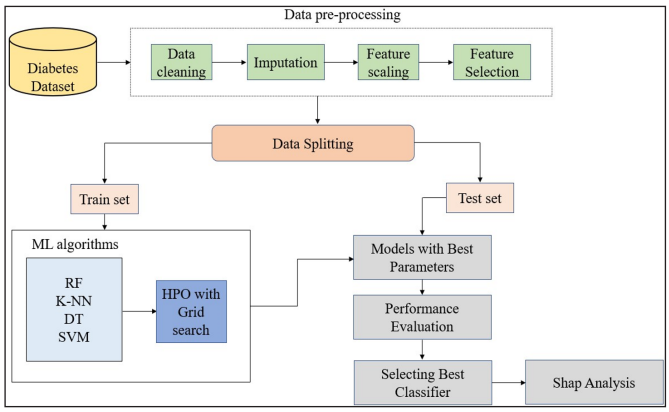

Figure 2. The flowchart of suggested predictive model for diabetes mellitus

Dataset

The approach developed within the scope of the study for the detection of DM is studied on the PIMA INDIANS (PIMA) data set. This dataset was originally created by the National Institute of Diabetes and Digestive and Kidney Diseases. It is open and accessible from the University of California, Irvine UCI AI repository. There are a total of 768 samples in the dataset, 500 from the non-diabetic class and 268 from the diabetic class. This dataset comprises eight independent and one output attributes. The output attribute has two classes, where '0' represents non diabetic and '1' represents diabetic.[20]

Data Pre-processing

Data preprocessing is the first stage to make the diabetes dataset raw data available for the prediction process. The data pre-processing stage consists of data cleaning, imputation, feature scaling and feature selection. In the data cleaning phase, operations such as cleaning the outliers detected in the data set, removing or completing the missing data are performed. These operations reduce the noise on the data. **Table 1** presents the statistical characteristics of the attributes in the data set. When the dataset was examined, it was seen that there were no missing values in the dataset and some attributes had zero values. In general, the Glucose, Insulin, BMI and blood pressure range can never start from zero values. Therefore, imputation process is required to fill the missing values. Imputation is a technique to replace missing data with some substitute values to preserve most of the data/information in the dataset.[21] Values with missing data in the data set were filled using the mean and median values of the features. In the next step, the feature scaling process is applied to the data sets whose missing data are completed. Feature scaling is one of the essential issues in preprocessing process before fitting it into the ML algorithms. This process can make a weak ML algorithm a better one. In this study, Min-max scaling technique is utilized for feature scaling. The principle this technique is illustrated in **Equation 1**. In this method, the largest and smallest values in a data set are taken into account. All other data are normalized to these values.[22]

Table 1. The statistical characteristics of the attributes in the PIMA INDIANS Diabetes Dataset

Attributes	Mean	Std.	Min	Max	Zero values
Pregnancies	3.84	3.37	0	17	0
Glucose	120.89	31.97	0	199	5
Blood pressure	69.1	19.35	0	122	35
Skin thickness	20.53	15.95	0	99	227
Insulin	79.8	115.24	0	846	374
Body mass index	32	7.88	0.07	67.1	11
Diabetes pedigree function	0.47	0.33	21	2.42	0
Age	33.24	11.76	0	81	0

$$X = \frac{x - \min(x)}{\max(x) - \min(x)}$$

The last step is selection of relevant feature. This process aims to reduce the number of attributes when building a predictive model.[19] In this study, the statistical correlations are used to identify critical features that could contribute significantly to ML algorithm and to achieve optimum performance. Correlation is utilized to measure the strength of the relationship between two attributes that are required in real life. Thus, it can predict the value of a variable with the help of other attributes associated with it. It is a type of bivariate statistics. The correlation matrix is defined as a table of all bivariate or zero-order correlations between and among the attributes in the dataset.[23] A correlation heatmap plot for feature selection is presented in **Figure 3**. It depicts shows correlations between and among all relevant features.

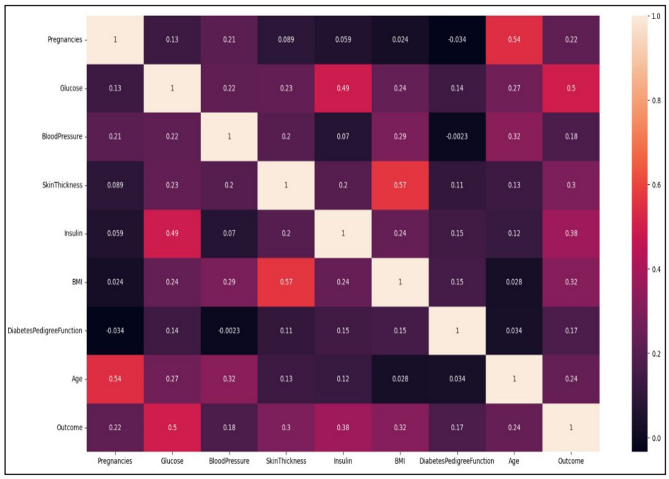

Figure 3. The correlation heatmap for feature selection

From the **Figure 4**, it can see a glimpse that the magnitude of correlation between "Outcome" output attribute and the independent attributes. The correlation coefficients are shown between output attribute and the independent attributes are shown in **Figure 5**. It can be clearly that the BP and DPF correlation sizes are less than "0.2" that is a low correlation with the outcome. Therefore, blood pressure (BP) and diabetes pedigree function (DPF) are eliminated from the primary diabetes dataset. Finally, after the feature selection process, the pregnancies, glucose, skin thickness (ST), insulin, body mass index (BMI) and age attributes are determined as the most relevant.

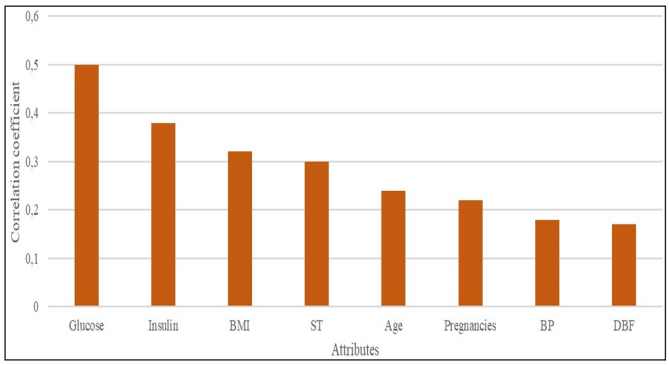

Figure 4. The correlation coefficients are shown between output attribute and the independent attributes

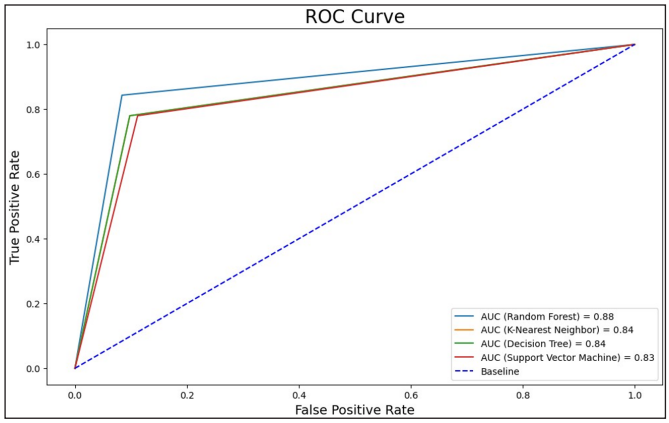

Figure 5. AUC-ROC Curve

Splitting the Dataset

Data splitting divides existing data into two parts. The first is used as training data to build a predictive model while the other is used as test data to evaluate the performance. In this study, 10-fold stratified cross validation (SCV) method is utilized as data splitting approach. SCV is an enhanced version of the k-fold CV. In k-fold CV, the dataset is divided into k subsets of equal size and samples are randomly selected for each subset or layer. Each subset is used for testing in turn and the rest is used for the training set. The model is evaluated k times model which each subset is utilized once as the test. Nevertheless, each subset is stratified so they contain approximately the same proportion of class labels as the original dataset during using SCV. Thus, the variance between predictions is diminished and the mean estimate error becomes more reliable.[24]

Machine Learning Algorithms

Because of the preprocessing step and the training/test sets partition, we processed it to fit the ML algorithms. Therefore, this section discusses the multiple supervised learning algorithms selected in this study to classify individuals with and without diabetes. Four classification algorithms used for predictions: RO, DT, K-NN and SVM. Grid search approach is utilized to automatically select the best hyperparameter for the ML algorithms. DT builds a structure a decision tree using the attributes in the dataset. This algorithm is utilized to predict classes based on the values of the attributes in the dataset. The tree starts from a root node and branches according to the characteristic of the dataset. Each branch contains a link between a property and possible values for that property. Each leaf node is associated with a class or output value. The K-NN algorithm looks at the K number of data points closest to that data point to estimate the class or value of a data point. SVM aims to find a function that can parse the training data using class labels. Since class labels are often called "yes-no" or "positive-negative", the most appropriate separator between these expressions, namely the hyperplane. In other words, SVM two decisions maximizes the distance between the boundary and the optimal separator aims to find the hyperplane. RF is formed by combining many DT. Each tree is applied to a subset of the dataset and its outputs are combined to make classification. The algorithm creates decision trees by choosing a random subset of the variables in the dataset. This helps prevent overfitting and increases generalization. Also, each tree has a different structure due to the selection of different subsets, resulting in greater diversity.[25]

Grid Search

Grid search approach is the one of most used hyperparameter optimization methods. It is a technique used in hyperparameter tuning to find the values that give the best performance in a given model. In this technique, the model is trained with all combinations of parameters given by the user, and it is an important process as the best parameters found affect the performance of the whole model. However, overfitting may occur during the optimization process. The overfitting problem can be reduced by applying the CV method. The CV technique trains a model with a dataset and tests it with various datasets. To determine the best combination of learning, Grid search with CV (GSCV) is utilized. Then, the set of parameter combinations with the highest accuracy is selected for each algorithm. After the selection of the best parameter set, the estimation process of the data begins. Using the k-fold CV technique, the dataset splits into training and testing part. 10-fold CV method is utilized in order to ten different sets of training and test. 10-fold CV method is utilized for each dataset to determine the average of diabetes prediction. With using the grid search and CV model together, hyperparameter optimization is obtained as a result of various experiments.[26]

Shapley Additive Explanations (SHAP) Analysis

Selecting the right algorithm with the right data has positive effect on the result in ML applications. ML algorithms takes the inputs and produce an output. Although the performance of the outputs can be measured by various techniques, the results are closed to make interpretation. In short, a black-box processed the data and produce an output. Explainable artificial intelligence methods can be applied to understand what is inside this black box mechanism. SHAP is one of these methods thar allows the ML model to be interpreted as a black box and not to be a black box. This method utilizes a game theory to identify ML algorithms. In this theory, the extent to which each player influences the game can be measured. In ML algorithms, it is possible to measure how much each attribute affects the result. In classification models using the SHAP technique, it can also be observed to what extent the features affect the result according to the classification type.[27]

Performance Evaluation Metrics

Evaluating the success of the models created in ML problems means determining the prediction success of the models. The confusion matrix is used to evaluate the relationship between the actual output values and the predicted values obtained after applying the models. From the confusion matrix, different performance metrics can be produced. The accuracy metric expresses the overall success of the model. Accuracy value, true number of classified samples divided by the total number of samples is obtained with. Precision, predicted positively how many of the values are actually positive metric showing diabetes disease. Also, the precision metric demonstrates the classifier's ability to eliminate false positives. Recall is expressed as a measure of ability to predict TP. F1-score is utilized to express the balance between precision and recall. One of the success evaluation criteria of classification models is ROC (Region of Curve). It explains how good the algorithm is at predicting. The area under the ROC Curve (AUC) can be considered as a summary of model ability, in other words, model performance.[28]

RESULTS

The hyperparameters of each algorithm, their search ranges and best combinations of hyperparameters of algorithms are shown in Table 2.

Table 2. The hyperparameters of each machine learning algorithms, their search ranges and best combinations of hyperparameters of machine learning algorithms

Algorithm	Hyperparameters	Search Range	Best Parameter
RF	"N_estimators"	[100, 200, 500,1000]	500
	"Max_features"	[3-7]	7
	"Min_samples_split"	[2-30]	5
	"Max_depth"	[3, 5, 8]	5
	"Min_samples_leaf"	[2-10]	5
K-NN	"N_neighbors"	[1-31]	5
DT	"Max_feature"	["auto", "sqrt", "log2"]	"log2"
	"Ccp_alpha"	[0.1, 0.01, 0.001]	0,01
	"Max_depth"	[5-9]	6
	"Criterion"	"entropy", "gini"	"entropy"
SVM	"C"	[1, 10, 100, 1000]	10
	"Gamma"	[1, 0.1, 0.01, 0.001, 0.0001]	0,1
	"Kernel"	["rbf", "linear"]	"rbf"

The prediction performances of used ML algorithms in DM diagnosis Table 3.

Table 3. The prediction performance of machine learning algorithms for diabetes mellitus

Algorithm	Accuracy (%)	Precision (%)	Recall (%)	F1-Score (%)
RF	89.06	84.33	84.33	84.33
K-NN	85.94	81.01	77.99	79.47
DT	85.42	79.54	78.36	78.95
SVM	85.02	78.87	77.99	78.42

AUC-ROC is one of the performance metrics used to evaluate the success of ML algorithms that explains how much algorithm distinguish between classes. Figure 5 illustrates the AUC-ROC curve for the ML algorithms.

DISCUSSION

Because diabetes is a worldwide public health threat, many researchers have motivated to develop ML applications to automate diabetes diagnosis as much as possible. In this study, different ML algorithms are used on a data set to detect diabetes. 10-fold SCV is used to for train-test split process. Hyperparameters of ML algorithms were determined by grid search 10-fold CV method. Data preparation, data preprocessing, creation of ML algorithms, statistical analyzes were performed using the Python program and its libraries. This study aims to compare the performance four different ML algorithms for diabetes prediction. The results obtained in terms of performance evaluation criteria of ML algorithms are presented in **Table 3** and **Figure 5**. In the first algorithm of this experiment is RF. In the RF algorithm, the result scored by applying GSCV method of best parameter the performance metrics of accuracy, precision, recall, F1-score and AUC-ROC is 89.06%, 84.33%, 84.33%, 84.33% and 0.88 respectively. The results obtained with the best parameters as a result of the hyperparameter optimization process of the K-NN used as the second algorithm is 85.94% of accuracy, 81.01% precision, 77.99% of recall, 79.47% of F1-score and 0.84 of AUC-ROC. The third ML algorithm used for diabetes prediction in the study is DT that shows 85.42%, 79.54%, 78.36%, 78.95% and 0.84 scores for performance evaluation metrics, respectively. The final ML algorithm SVM tested in this experiment achieves 85.02% accuracy, 78.87% precision, 77.99% recall, 78.42% F1-score, and 0.83 AUC score. When comparing the classification rates of ML, RF shows the best predictive ability to predict diabetes.

Clinical decisions that can be taken with ML algorithms in the field of health are important for the lives of patients. It is useful to have both accurate and interpretable prediction models in these applications. Therefore, to interpret the model, the SHAP technique can be used to discover the importance of each feature in determining the predicted output. The model can be interpreted based on the SHAP values that explain the contribution of each feature to the prediction. **Figure 6** shows the feature importance for the prediction of DM, and the contribution of each attribute to the performance of the algorithm. This figure depicts the SHAP values for the RF algorithm with the highest prediction rate.

According to this graph, "Insulin", "Age", and "Glucose" attributes contributed the most to the prediction model in identifying patients with diabetes. It is seen that the least contributing attributes are "Pregnancies", "BloodPressure" and "BMI".

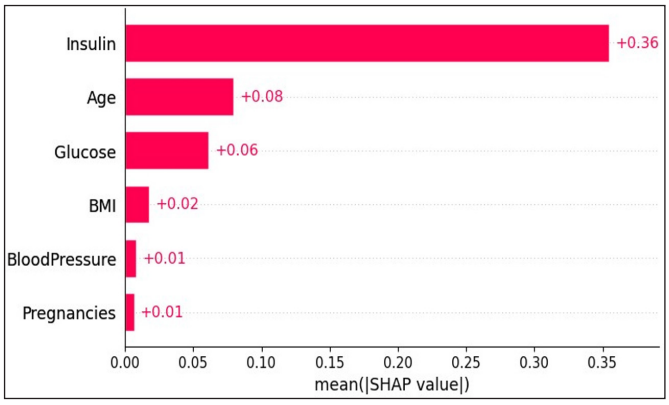

Figure 6. SHAP values of the RF algorithm

The comparison of the model proposed in this study with similar studies in the literature with the same data set are presented in **Table 4**. When similar studies in the literature are examined, it is seen that the models proposed for the prediction of DM reach accuracy rates between 75-90%. The GSCV-RF model proposed in this study also has a good prediction rate as a result of the comparison.

Table 4. Comparison of the suggested model with the similar studies in the literature

References	Year	Methods	Accuracy (%)
Birjais et al.[9]	2019	GB	86
Sing & Sing[11]	2020	Stacked ensemble approach	83.8
Lyngdogh et al.[12]	2021	K-NN	76
Kumari et al[13]	2021	SVC	79.08
Chang et al.[14]	2022	RF	82.26
Yakut[15]	2023	RF	81.77
Our proposed		GSCV+RF	89.06

The model suggested in this study was tested on an open access diabetes dataset. This situation is the most important limitation of our study. It is planned to predict the diabetes disease that may develop over time with high sensitivity and accuracy by using the clinical data, genetic data, past hospital visit data and current patient findings in the open access diabetes dataset that we used as a prototype in our study.

CONCLUSION

ML algorithms can enable the diagnosis of diseases by using datasets obtained in the field of health. In this study, an approach using ML algorithms for the diagnosis of diabetes, which is an important health problem worldwide, is proposed. The classification process is conducted by using four different ML algorithms on a diabetes dataset which is widely used in the literature. Since the data set used does not have a balanced bit structure, a series of data preprocessing steps were applied. The RF, K-NN, DT and SVM algorithms used in the study contain many hyperparameters. Choosing

the right combination of hyperparameters increases the success rate of ML algorithms. For this reason, GSCV method is used to select the most suitable hyperparameters of ML algorithms. The classification rates of the algorithms are evaluated with different performance criteria. As a result of the comparisons, the GSCV-RF model achieves the highest classification rate, with 89.06%, 84.33%, 84.33%, 84.33% and 0.88 accuracy, precision, sensitivity, F1-score and AUC-ROC. In this study, unlike the studies in the literature, the extent to which the attributes in the data set affect the result is investigated using SHAP analysis. The order of importance of the qualities that have an impact on the success of the model has been revealed in terms of interpreting this established model from the perspective of a healthcare professional. As a result of this analysis, it can be concluded that "Insulin", "Glucose", "Age" parameters have significant place in the diagnosis of diabetes. In this study, an ML estimator tool is presented to identify diabetic and non-diabetic individuals with high accuracy. It is thought that hospitals or diabetes prevention programs can benefit from the suggested approach.

ETHICAL DECLARATIONS

Ethics Committee Approval: Not applicable. An opensource dataset was utilized for the study.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

MEDICINE PALLIATIVE CARE

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Increased frequency of hypertension and coronary artery disease independent of age in primary hyperparathyroidism associated hypercalcaemia

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ABSTRACT

Aims: There are conflicting data in the literature regarding whether there is an increased frequency of coronary artery disease (CAD) in patients with primary hyperparathyroidism (PHP). In this study, we planned to investigate the frequency of CAD and hypertension (HT) in patients with PHP.

Methods: Patients with PHP aged 18 years and older who were admitted to the endocrinology clinic between September 2020 and February 2023 were included as the patient group, and age- and gender-matched individuals who presented with thyroid nodules between the same dates were included as the control group. A total of 217 patients, 114 with PHP and 103 as control group, were eligible for the study. The study was conducted as a retrospective data analysis and laboratory and demographic information of the patients and the control group were obtained from their files.

Results: Age and gender distribution of the patient group and the control group were similar (respectively; age: 55.6+12.9 years, 53.0+7.2 years, p=0.058, female/male distribution: 93/21, 80/23 p=0.48). The prevalence of HT and CAD was higher in the patient group (respectively; HT: 65.1%, 31.0%, p<0.001, CAD: 32.0%, 3.1%, p<0.001), while the prevalence of DM was similar (respectively; 18.1%, 17.3%, p=0.89). The prevalence of HT, CAD and DM was found to be the same among those with mild and severe PHP (respectively; HT: 65.6%, 64.4%, p=0.90, CAD: 38.3%, 23.3%, p=0.14, DM: 19.7%, 15.9%, p=0.62,). Age (β=0.10, odds ratio [OR];1.11 [95% confidence interval (95% CI);1.05-1.17], p<0.001) and calcium (β=0.67, OR;1.96 [95% CI;1.10-3.51], p=0.023) levels were found to be independent effective factors on CAD.

Conclusion: Increased calcium levels in PHP constitute an age-independent risk for CAD. In addition, elevated calcium increases the frequency of HT, which is a CAD risk factor.

Keywords: Primary hyperparathyroidism, hypertension, coronary artery disease, hypercalcaemia

INTRODUCTION

Primary hyperparathyroidism (PHP) is one of the most common endocrine hormone hypersecretions.[1] The diagnosis is made with the presence of normal or increased parathyroid hormone (PTH) levels despite increased plasma calcium (Ca) levels.[2] Increased laboratory use in daily practice has led to more frequent encounters with hypercalcaemia and PHP.[3] Since there is no known effective medical treatment for PHP, the only treatment is surgical resection of the abnormal parathyroid gland.[2] However, due to widespread laboratory use, a significant proportion of patients are detected at an asymptomatic stage that does not require surgery.[3] Indications for surgical operation in individuals with asymptomatic PHP are as follows: younger than 50 years of age, Ca levels increased by 1 unit in mg/dL compared to the upper limit of normal, increased urinary Ca (U Ca) level (400 mg/day), presence of osteoporosis or osteoporosis-related fracture, glomerular filtration rate <60 ml/min, kidney stones or nephrocalcinosis.[4]

Investigation of the relationship between increased PTH hormone levels and cardiovascular diseases and hypertension (HT) has a history of more than 30 years.[5] In the first studies, it was found that increased PTH levels in vitro increased aldosterone and cortisol secretion from adrenal cortex cells.[5] Later studies revealed that PTH-like peptide (PTHrp) structure has a similar effect.[6,7] The relationship between PTP and HT found in in vitro studies was also demonstrated clinically in the following years.[8,9] Improvement in HT and hyperaldesteronism in the postoperative period has been found in studies.[10,11]

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While there are studies in which no relation between PHP and CAD was found,[12] there are also studies in which a relation between PHP and CAD was found.[13] Despite the increased frequency of HT, the presence of HT in asymptomatic patients does not yet constitute an indication for operation in the guidelines.[4] The primary reason for this seems to be conflicting data on whether the frequency of cardiovascular disease increases in PHP.[10]

In this study, it was planned to investigate the relationship between PTH and Ca and the frequency of cardiovascular disease and HT in individuals with PHP.

METHODS

The study was carried out with the permission of Bursa City Hospital Clinical Researches Ethics Committee (Date: 05.04.2023, Decision No: 2023-5/12). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was conducted as a retrospective data review and individuals with PHP who were admitted to the endocrinology, diabetes and metabolic diseases clinic of University of Health Sciences Bursa City Hospital between September 2020 and February 2023 were included in the study.

Inclusion Criteria

18 years and over, diagnosed with PHP

Exclusion Criteria

Familial hypocalciuric hypocalcaemia, secondary and tertiary hyperparathyroidism, pregnant women, those receiving treatment for systemic diseases other than DM, HT and CAD.

Study Design and Work Plan

Plasma Ca, phosphorus (P), PTH, creatinine (Cr), glomerular filtration rate (GFR), vitamin D3 (VitD3), UCa, albumin, thyroid stimulant hormone (TSH), low density lipoprotein, information on age, height, weight, bone density measurement (dual-energy x-ray absorptiometry [DEXA]), medications, diabetes mellitus (DM), HT and CAD were obtained from patient files. Body mass index (BMI) was calculated as kilogram/m², corrected Ca (mg/dL) was measured as total serum Ca, corrected by 0.8 mg/dL for every 1 g/dL change in serum albumin concentration of the patient relative to 4.0 g/dL.

The diagnosis of PHP, differentiation between PHP and familial hypocalciuric hypercalcaemia, and differential diagnosis of normocalcaemic PHP and secondary hyperparathyroidism were made in accordance with the recommendations of the current guidelines.[4,14] According to the current guidelines, patients whose plasma Ca levels increase less than 1 mg/dL compared to the upper limit of normal are defined as mild PHP and those with an increase of 1 mg/dL and above are defined as severe PHP.[14]

The presence of CAD was considered as stent implantation after previous percutaneous catheterisation or hospitalisation due to acute myocardial infarction (aMI) and necessary information was obtained from patient files and recorded as CAD present/absent. Those with a current diagnosis of HT were checked whether they had been prescribed anti-HT medication in the last 3 months from the electronic prescription system, and HT status was recorded as present or absent.

Age and gender matched patients who were followed up for euthyroid thyroid nodule were selected as control group.

Statistical Analysis

After the normal distribution was determined by Kolmogorov-Smirnov test, an independent samples t-test was applied to data with a normal distribution. The Pearson's chi-squared test was used to compare ratios. Pearson and Spearman tests were used to determine the correlation between the data, Binary logistic regression analyses were used to determine whether the correlated data were independent factors. A p-value of less than 0.05 was considered statistically significant. IBM® Statistical Package for the Social Sciences (SPSS) statistics 20 was used to compare the data.

RESULTS

A total of 217 patients, 114 with PHP and 103 as control group, were eligible for the study. Both PHP and control group and mild and severe PHP groups were compatible with each other in terms of age, BMI and sex ratios (Table 1 and Table 2).

Table 1. General characteristics and laboratory properties of PHP and control group

	Control group (103)	PHP (114)	p
Age (year)	53.0+7.2	55.6+12.9	0.058
Female/male	80/23	93/21	0.48
BMI (kg/m²)	29.47	28.44	0.23
Creatinine (mg/dL)	0.74+0.20	0.78+0.26	0.17
Ca (mg/dL)	9.3+0.39	11.80+0.96	<0.001
P (mg/dL)	3.6+0.45	2.30+0.48	<0.001
PTH (ng/L)	34.5+16.0	227.1+158.9	<0.001
Vit D3 (ng/mL)	20.16+11.08	15.07+7.93	<0.001
TSH (uIU/mL)	3.06+10.30	1.61+1.09	0.17
LDL (mg/dL)	126.89+37.29	115.42+26.13	0.011
DEXA			
L1-4 (T score)	-	-1.85+1.61	
Femur total (T score)	-	-1.48+1.08	

BMI: Body mass index, Ca: Calcium, P:Phosphorus, PTH: Parathyroid hormone, Vit D3: Vitamin D3, TSH: Thyroid stimulant hormone, LDL: Low density lipoprotein, DEXA: Dual-energy x-ray absorptiometry, L1-4: lumbar spine 1-4.

Table 2. General characteristic and laboratory features of the mild and severe PHP group

	Mild PHP (53)	Severe PHP (61)	p
Age (year)	56.1+11.9	55.2+13.8	0.72
Female/male (n)	46/7	47/14	0.18
BMI (kg/m²)	28.51+5.58	28.37+4.37	0.91
Creatinine (mg/dL)	0.67+0.14	0.86+0.28	<0.001
Ca (mg/dL)	11.01+0.29	12.36+0.88	<0.001
P (mg/dL)	2.09+0.45	2.63+0.33	<0.001
PTH (ng/L)	156.2+68.0	277.1+184.3	<0.001
Urinary Ca (mg/day)	326.3+148.6	355.6+163.8	0.35
Vit D3 (ng/mL)	15.3+7.2	14.9+8.5	0.77
TSH (µIU/mL)	1.67+1.05	1.58+1.11	0.68
LDL (mg/dL)	116.78+25.34	114.27+26.94	0.61
DEXA			
L1-4 (T score)	-1.64+1.54	-2.02+1.67	0.26
Femur total (T score)	-1.32+1.21	-1.59+0.97	0.27

BMI: Body mass index, Ca: Calcium, P: Phosphorus, PTH: Parathyroid hormone, Vit D3: Vitamin D3, TSH: Thyroid stimulant hormone, LDL: Low density lipoprotein, DEXA: Dual-energy x-ray absorptiometry, L1-4: lumbar spine 1-4.

Clinical Findings

The frequency of HT, CAD and kidney stones were higher in patients with PHP compared to the control group, on the other hand the frequency of DM was similar (Figure 1 and Figure 2).

The general characteristics and laboratory parameters of the study group with PHP and the control group are shown in Table 1. The frequency of HT (64.4%, 31%, p<0.001, respectively), CAD (23.3%, 3.1%, p<0.001, respectively) and kidney stones (26.2%, 3.1%, p<0.001, respectively) were higher in patients with mild PHP compared to the control group, whereas the frequency of DM was similar (15.9%, 17.3%, p=0.83, respectively).

Comparison of clinical and laboratory characteristics of patients with mild PHP and severe PHP is given in Table 2.

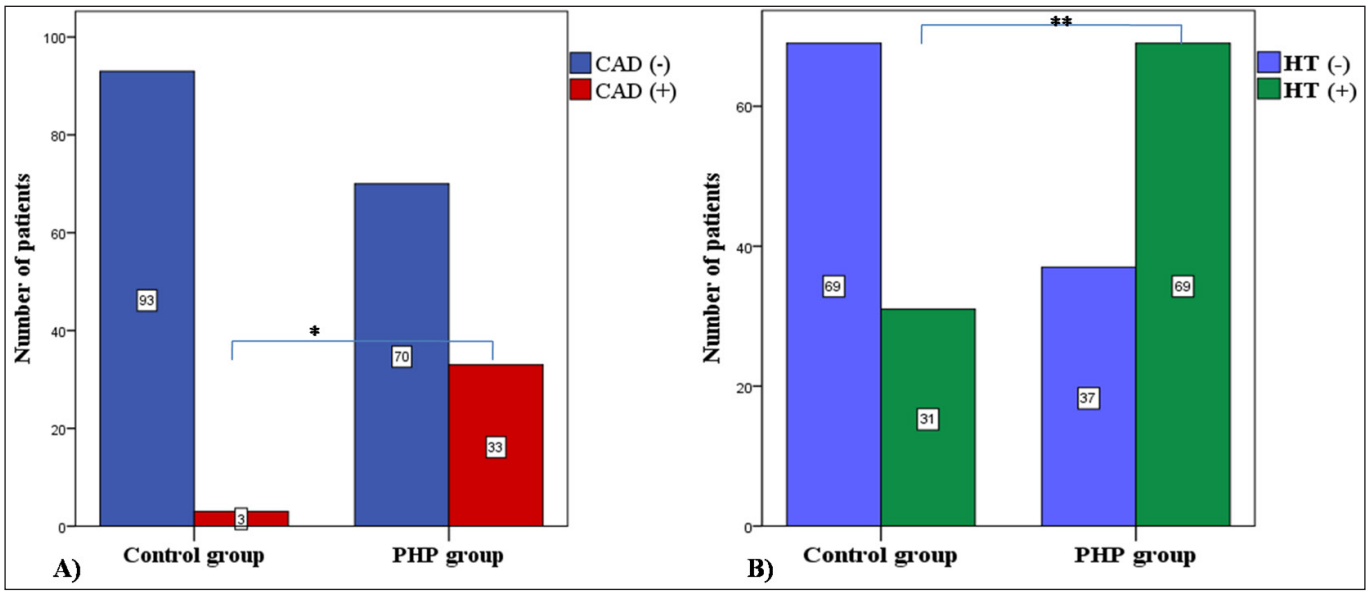

Figure 1. Prevalence of CAD (A) and HT (B) in the patient group and control group (*p<0.001, **p<0.001).

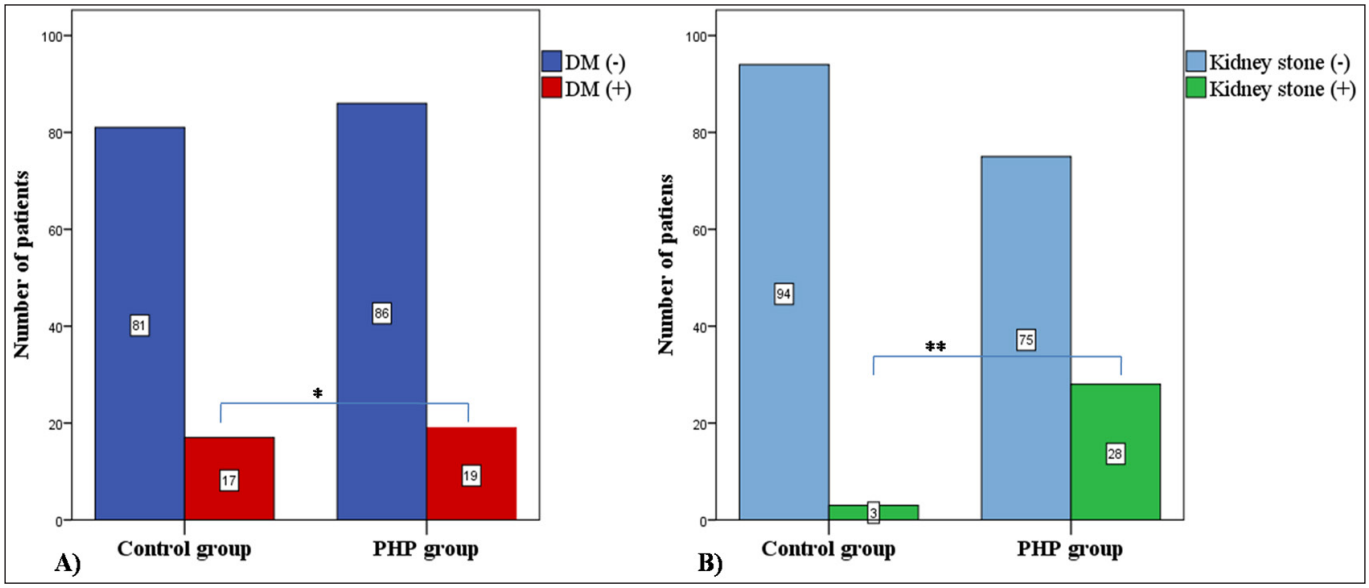

Figure 2. Frequency of DM (A) and kidney stone (B) in the patient group and control group (*p=0.89, **p<0.001).

Laboratory

The laboratory characteristics of the study and control groups are shown in Table 1.

While there was a difference between the Ca levels of those with CAD and those without CAD (11.6+1.2 mg/dL, 10.4+1.4 mg/dL, p<0.001, respectively), there was no difference between the PTH levels (249.7+142.7, 188.2+168.7, p=0.054, respectively).

When plasma Ca levels of patients with kidney stones were compared with plasma Ca levels of patients without kidney stones, it was observed that plasma Ca levels were higher in the group with kidney stones (11.9+1.3 mg/dL, 10.3+1.3 mg/dL, p<0.001), PTH levels (225.4+198.4 ng/L, 198.0+150.8 ng/L, p=0.50, respectively) and U Ca (337.11+138.21 mg/day, 342.24+169.17 mg/day, p=0.88, respectively) were similar between the two groups.

Plasma Ca levels of HT patients were higher than non-HT patients (11.1+1.5 mg/dL, 10.1+1.3 mg/dL, p<0.001, respectively), and PTH levels of HT and non-HT patients were not different (225.3+144.5 ng/L, 173.3+182.7 ng/L, p=0.10, respectively).

Correlation and Regression Analysis

A correlation was found between CAD with Ca and PTH levels (Table 3).

Table 3. Parameters that correlate with HT, DM and CAD

HT	DM	CAD
Age (r=0.42, p<0.001)	Age (r=0.21, p=0.002)	Age (r=0.39, p<0.001)
Gender (r=0.08, p=0.24)	Gender (r=0.08, p=0.27)	Gender (r= -0.06, p=0.42)
Ca (r=0.33, p<0.001)	Ca (r= -0.10, p=0.89)	Ca (r=0.42, p<0.001)
PTH (r=0.16, p=0.09)	PTH (r= -0.09, p=0.31)	PTH (r=0.17, p=0.07)
DM (r=0.33, p<0.001)	CAD (r=0.15, p=0.035)	DM (r=0.15, p=0.035)
CAD (r=0.47, p<0.001)	HT (r=0.33, p<0.001)	HT (r=0.47, p<0.001)

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, Ca: Calcium, PTH: Parathyroid hormone.

Logistic regression analysis showing the effect of independent variables on CAD is shown in Table 4. Age and Ca levels stand out as independent factors effective on CAD (Table 4).

DISCUSSION

Present study, it was found that the frequency of CAD and HT increased in PHP and hypercalcaemia was an effective factor on both the presence of CAD and HT. There was no association between PTH levels and HT and CAD.

One of the results obtained from our study was that the frequency of HT was higher in both mild and severe PHP. In present study, the prevalence of HT was found to be 31.0% in the control group and 65% in the PHP group and was compatible with the general literature.[15,16] In the study of Luigi[17] and colleagues (et al.), the prevalence of HT in PHP was found to be 81%, which was much higher than the general literature data.[16] The reason for this may be the small number of patients in the study of Luigi et al. Current guidelines[2,4] do not include HT among the indications for surgery in PHP. In the same guideline, it is stated that the results related with cardiovascular disease are not different between those with and without surgery and HT cannot be a reason for operation indication yet, due to reasons such as the persistence of HT in a significant proportion of operated patients.[2] PHP has been shown to cause increased activity in the renin aldosterone system both in vitro[5-7] and in clinical studies,[18] and improvement in the renin aldosterone system has been found after surgical treatment.[19] The approach regarding HT in PHP should not be all or none. In PHP, there is a study showing improvement in HT 6 months after surgery,[20] as well as a significant decrease in the frequency of HT and a decrease in the non-dipping pattern in the study by Luigi et al.[17] In another study, a decrease in both mean blood pressure and the number of drugs used was observed.[21] In the study by Beysel et al.[22] a decrease in systolic and diastolic blood pressure

Table 4. Independent variables affecting HT and CAD in logistic regression analysis

Dependent variable	Independent variable	β	Wald Chi-square	p	OR	OR (*95% C.I.)	
						Lower	Upper
	Constant	-14.48	14.16	<0.001	0.00		
Model 1	Age	0.10	13.93	<0.001	1.11	1.05	1.17
CAD	Ca	0.67	5.18	0.023	1.96	1.10	3.51
	PTH	0.001	0.10	0.76	1.01	0.99	1.04
	DM	0.73	1.41	0.24	2.07	0.62	6.87
	Gender	-0.66	1.06	0.30	0.52	0.15	1.82
	Constant	-13.25	12.79	0.00	0.000		
Model 2	Age	0.11	18.14	<0.001	1.12	1.06	1.18
HT	Gender	0.12	0.04	0.84	1.13	0.35	3.69
	Ca	0.61	4.63	0.03	1.85	1.06	3.22
	PTH	0.001	0.31	0.58	1.00	0.99	1.01
	DM	2.35	4.62	0.03	10.43	1.23	88.52

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, PTH: Parathyroid hormone, * 95% C.I.: Confidence interval.

was found postoperatively in both normocalcaemic and hypercalcaemic PHP patients, and improvement was also found in parameters considered as cardiovascular risk factors in the same study. One of the biggest problems here is whether the detected HT is essential HT or HT triggered by PHP. This distinction does not seem to be easy for now. Nevertheless, it may be more appropriate for the guidelines to reconsider their decision on the surgical indication for HT in PHP and to evaluate this situation not from an all-or-nothing point of view, but from a broader perspective based on whether HT is under control or not, or from a broader perspective based on the number of medications and whether it is under control with the current medications or not, or even whether it is under control or not despite the fact that one of the medications contains a potassium-sparing diuretic. However, this issue is still unclear and additional studies are needed in this field.

Another result obtained from this study was that the frequency of CAD was increased in patients with both mild and severe PHP. Factors such as increased blood pressure in PHP,[16] endothelial dysfunction,[23] hyperactivity in aldosterone-renin-angiotensin system,[5,6,18,19] insulin resistance and deterioration in metabolic parameters[22] may be considered as the reason for this increase. There are many studies showing an increase in total mortality and CAD in PHP.[24-26] Current guidelines do not indicate the presence of CAD in PHP as an indication for surgery for the time being,[2] again citing the lack of a decrease in CAD-related mortality after surgery in PHP and the fact that CAD-related mortality may increase in some patients after surgery.[24] On the other hand, a decrease in blood pressure,[17] improvement in endothelial dysfunction[23] and insulin resistance,[22] hyperactivity in aldosterone-renin-angiotensin system,[18] and CAD-related mortality[24] are observed after surgery in PHP. Although an association between CAD and mortality has been found in PHP, there are still unanswered questions, one of which is whether there is an increase in asymptomatic patients, and the other is whether it is hypercalcaemia or hyperparathyroidism that causes this. Lundgren et al.[27] found a relationship between increased calcium levels and CAD and mortality in a 20-year follow-up. In another study, it was observed that patients with chronic renal failure (CRF) and normal Ca levels but secondary hyperparathyroidism (SHP) had a higher rate of non-dipping pattern compared to patients with normal PTH levels.[28] In the study by Wang et al.[29] among patients with CRF and SHP on haemodialysis programme, improvement in blood pressure was observed in those who underwent parathyroidectomy, whereas an increase in diastolic blood pressure was observed in those treated with cinecalcet. As can be seen, the situation is intertwined and complicated. In present study, an association was found between Ca levels and CAD, but no association was found between CAD and HT and PTH. Randomised controlled studies are needed to clarify this issue.

Our study has some limitations; firstly, there may be deficiencies in the collection of some data due to its retrospective design, for example; smoking status, post-operative hypertension status, patients family history of CAD and and physical activity of patients. Secondly, mortality data could not be obtained in our study and therefore the effect of mild hypercalcaemia on mortality could not be evaluated. Thirdly, data on the number of anti-hypertensive drugs used could not be obtained.

CONCLUSION

Increased calcium levels in PHP are associated with HT regardless of the amount of increase, and increased Ca levels have an age-independent effect on the presence of CAD disease. No independent association was found between PTH levels and either HT or CAD. In this case, the answer to the question of whether PTH or increased Ca levels are responsible for cardiovascular events in PHP seems to be in favour of increased Ca levels. However, this issue needs to be supported by additional studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bursa City Hospital Clinical Researches Ethics Committee (Date: 05.04.2023, Decision No: 2023-5/12).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Awareness and rates of vaccination in hemodialysis patients

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ABSTRACT

Aims: Vaccination is main risk reducing strategy for vaccine-preventable infections in chronic kidney disease (CKD) patients, but vaccination rates in hemodialysis patients are not at the desired level. In this study, we aimed to search the rates of influenza, pneumococcal, hepatitis B and coronavirus disease-2019 (COVID-19) vaccination, the vaccination awareness and the reasons for not taking vaccination in hemodialysis patients.

Methods: In this cross-sectional study, 232 CKD patients undergoing hemodialysis in two centers for at least six months were included. The patients completed the questionnaire about vaccination. The data about patients' history of vaccination regarding influenza, pneumococcal, hepatitis B and COVID-19 vaccines; patients' attitudes and knowledge about vaccination; the source of information about vaccination were collected via this questionnaire.

Results: The rates of pneumococcal, influenza, hepatitis B and COVID-19 vaccination were 9.9%, 56.6%, 38.8% and 87.1%, respectively. In patients with missing vaccination, the main reasons for not taking vaccination were lack of knowledge about vaccination (48.7%), the thought that the vaccine is not beneficial (12.5%) and fear of adverse effects (3.4%). The main sources of information about vaccination were healthcare workers (90.5%), radio/televison (1.7%) and internet (1.7%).

Conclusion: Our findings showed that the rates of influenza, pneumococcal and hepatitis B vaccination were below the targeted levels and the main reason was the lack of information about vaccination and the main source of information about vaccination was health personnel. Strategies should be developed to increase the awareness and rate of vaccination for vaccine-preventable infections in CKD patients.

Keywords: Awareness, hemodialysis, vaccination, chronic kidney disease

INTRODUCTION

Chronic kidney disease (CKD) is an important public health problem and it affects approximately 8-16% of adults worldwide.[1] CKD patients are more prone to infections. This may be due to impaired immune function, immunosuppressive therapies, dialysis-related causes, increased hospitalization rates, advanced age or comorbidities such as diabetes.[2,3]

In hemodialysis patients, infectious diseases are the second most common cause of mortality after cardiovascular disease; and infectious diseases, also, contribute to increased hospitalization rates.[2] Preventing a disease is always much more effective, easier and cost-effective process than treatment of it. Vaccination is among the most tremendous discoveries in human history and it has saved millions of lives to date. It is one of the most effective tool to prevent infectious diseases in CKD patients.[4] Some infection types, such as hepatitis B, influenza and pneumococcal infections, are preventable via vaccinations. So, vaccine recommendations are main risk reducing strategy for vaccine-preventable infections in CKD patients.[3]

Influenza vaccination is important for high risk population such as older adults or individuals with chronic conditions; it reduces the risks of influenza infection-related complications by 20-40% in the general population with relatively reduced effectiveness in advanced CKD patients.[3] Annual influenza vaccination is recommended to all adult CKD patients who have no contraindication.[5]

Pneumococcal vaccination is effective to prevent infections caused by *Streptococcus pneumoniae*.[3] Pneumococcal vaccination and revaccination within 5 years, is recommended to adult patients with eGFR <30 ml/min/1.73 m².[5]

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Hemodialysis patients have increased risk for blood-borne pathogen exposure.[4] Hepatitis B virus (HBV) infection in hemodialysis patients tends to be chronic more often compared with that of non-uremic patients (30%-60% vs 10%).[2] The rates of HBV infection among hemodialysis patients can be decreased by vaccination and additional precautions, such as screening for hepatitis B in dialysis centers, decreasing transfusions by using erythropoietin, segregation of the equipment of seropositive patients.[2,4] CKD patients may have poor response to hepatitis B vaccine.[4] Immunization against HBV and the response confirmation by serological tests is recommended to CKD patients including hemodialysis patients.[5]

The development of Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) vaccination had important role in controlling spread of Coronavirus disease-2019 (COVID-19) infection and decreasing symptomatic form of disease.[6] Hemodialysis patients had increased risk of COVID-19 infection with increased hospitalization and mortality rates compared to general population and SARS-CoV-2 vaccination had protective role in this susceptible population.[7]

Although vaccination is most effective tool to prevent vaccine-preventable infectious diseases, it may be overlooked and vaccination rates in hemodialysis patients are still below the desired level and CKD patients remain somewhat under-vaccinated.[2,4] This may be due to efficacy concerns, ineffective reminder systems, time constraints, financial and health care access status, lack of knowledge or incorrect knowledge about vaccine (about its importance, adverse effects, etc.), or patients' thoughts about vaccines which may lead to vaccine rejection, reluctance or hesitancy.[2,8-10] There are limited number of study investigating the awareness about vaccination, attitude towards vaccination and the vaccination rates among hemodialysis patients. In this study, we aimed to search the rates of influenza, pneumococcal, hepatitis B and COVID-19 vaccination, the vaccination awareness, the reasons for not taking vaccination and the sources of information about vaccination among hemodialysis patients.

METHODS

The study was carried out with the permission of KTO Karatay University Faculty of Medicine Non-medicine and Non-medical Device Researches Ethics Committee (Date: 29.12.2022, Decision No: 2022/009). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written consent was obtained from the patients participating in this study.

In this cross-sectional study, CKD patients (aged >18 years) undergoing hemodialysis in two centers for at least six months were included and the study was carried out between January 1, 2023 and January 31, 2023. Patients with neurological or psychological disabilities or who could not answer the survey questions were excluded. Written informed consent was obtained from the patients participating in the study.

Patients' demographical and clinical data including age, gender, occupation, educational status, comorbidities, the date when hemodialysis was initiated, etiologies of CKD and laboratory findings were obtained from the patient files. The patients who met the inclusion criteria and who agreed to participate in the study completed the questionnaire form structured based on the objectives of this study. The data about socio-demographic characteristics of patients; patients' history of vaccination regarding influenza, pneumococcal, hepatitis B and COVID-19 vaccines; patients' attitudes and knowledge about vaccination; the source of information about vaccination were all collected via this questionnaire.

Statistical Analysis

Statistical analyses of data were performed using Statistical Package for Social Sciences for Windows version 22 (SPSS 22) program. Descriptive tests such as frequency and descriptive statistics were used to evaluate the data.Continuous variables were expressed as mean ± standard deviation, categorical variables were reported as frequency and percentage.

RESULTS

In this study, 232 hemodialysis patients (108 female, 46.6%; 124 male, 53.4%) were included. Patients' mean age was 57±14. Of the patients, 174 (75.0%) were married. The education level of 168 patients (72.4%) was primary school and 39 patients (16.8%) were illiterate. Data regarding patients' occupations were as follows: 102 patients (44.0%) were housewife; 52 patients (22.4%) were retired; 22 patients (9.5%) were unemployed; 36 patients (15.5%) were working in their own workplace; 20 patients (8.6%) were employee. Most of the patients (92.7%) lived in the city center; 17 patients (7.3%) lived in the village. CKD etiologies of these patients were diabetes mellitus (66 patients, 28.4%), hypertension (60 patients, 25.9%), polycystic kidney disease (18 patients, 7.8%), glomerulonephritis (10 patients, 4.3%), urological causes (18 patients, 7.8%), amyloidosis (2 patients, 0.9%) and unknown underlying etiologies (58 patients, 25.0%). Of the patients, 53 (22.8%) had smoking history. Demographic and clinical characteristics of the patients were summarized in **Table 1**.

Table 1. Demographic and clinical characteristics of the patients

Parameters	
Age, year, mean±SD	57±14
Gender, n (%)	
Female	108 (46.6)
Male	124 (53.4)
Marital status, n (%)	
Married	174 (75.0)
Single	58 (25.0)
Educational status, n (%)	
Illiterate	39 (16.8)
Primary school graduate	168 (72.4)
High school graduate	16 (6.9)
University graduate	9 (3.9)
Occupation, n (%)	
Housewife	102 (44.0)
Retired	52 (22.4)
Self-employed	36 (15.5)
Employee	20 (8.6)
Unemployed	22 (9.5)
Location, n (%)	
City center	215 (92.7)
Village	17 (7.3)
CKD etiology, n (%)	
Diabetes mellitus	66 (28.4)
Hypertension	60 (25.9)
Polycystic kidney disease	18 (7.8)
Urological causes	18 (7.8)
Glomerulonephritis	10 (4.3)
Amyloidosis	2 (0.9)
Unknown	58 (25.0)

SD, standart deviation; CKD, chronic kidney disease.

Regarding vaccination rates, 129 patients (56.6%) were vaccinated with influenza vaccine; 23 patients (9.9%) were vaccinated with pneumococcal vaccine; 202 patients (87.1%) were vaccinated with COVID-19 vaccine and 90 patients (38.8%) were vaccinated with hepatitis B vaccine and completed hepatitis B immunization schedule. Hepatitis B surface antigen (HBsAg) was positive in 5 patients (2.2%). Data regarding vaccinaton history of the patients were shown in Table 2.

Table 2. The rates of influenza, pneumococcal, hepatitis B and COVID-19 vaccination of the patients

Vaccine	n (%)
Influenza	
Vaccinated	129 (56.6)
Pneumococcal	
Vaccinated	23 (9.9)
Hepatitis B	
Vaccinated	90 (38.8)
Immune due to natural infection	85 (36.6)
HBsAg positive	5 (2.2)
COVID-19	
Vaccinated, at least one dose (or more)	202 (87.1)
Vaccinated, two doses	68 (29.3)
Vaccinated, three doses	74 (31.9)
Vaccinated, four doses	33 (14.2)
Vaccinated, five doses	14 (6.0)
Vaccinated, six doses	3 (1.3)

In patients with missing vaccination, the main reasons for not taking vaccination were lack of knowledge about vaccination (113 patients, 48.7%), the thought that the vaccine is not beneficial (29 patients, 12.5%), fear of adverse effects (8 patients, 3.4%), lack of information on vaccination timing (5 patients, 2.2%), having allergy (2 patients, 0.9%) and other reasons (56 patients, 24.1%) (Table 3).

Table 3. The reasons for not taking vaccination

	n (%)
Lack of knowledge about vaccination	113 (48.7)
The thought that the vaccine is not beneficial	29 (12.5)
Fear of adverse effects	8 (3.4)
Lack of information on vaccination timing	5 (2.2)
Having allergy	2 (0.9)
Other	56 (24.1)

The sources of information about vaccination were healthcare workers (210 patients, 90.5%), radio/televison (4 patients, 1.7%), internet (4 patients, 1.7%), family/relatives (3 patients, 1.3%), and other sources (11 patients, 4.7%) (Table 4).

Table 4. The sources of information about vaccination

	n (%)
Health personnel	210 (90.5)
Radio/television	4 (1.7)
Internet	4 (1.7)
Family/relatives	3 (1.3),
Other	11 (4.7)

DISCUSSION

Knowing the fact that prevention of a disease is always more effective and easier than treatment, vaccination is crucial for primary prevention and it is main risk reducing tool for vaccine-preventable diseases in CKD patients.[3] Vaccination rates in hemodialysis patients are not at the targeted level.[11,12] There are limited number of study about the vaccination rates and the awareness of vaccination in hemodialysis patients. In this study, the rates of pneumococcal, influenza, hepatitis B and COVID-19 vaccination were 9.9%, 56.6%, 38.8% and 87.1%, respectively. In previous studies, different rates of vaccination were reported in hemodialysis patients: In the study of Mutlu et al.[13] the rates of pneumococcal and influenza vaccination were reported as 14.4% and 51.4% respectively, whereas these rates in the study of Günay et al.[9] were 3.3% and 18.3%, respectively. These different findings between studies may be due to differences in the study population (different sample size or different socio-economical or educational status, etc.) and/or due to lack of standardized vaccination practice. In a study

from Nigeria, only 5.7% of patients had completed the hepatitis B vaccination schedule and this was attributed to poor awareness.[14] In the study of Günay et al.[9] rate of hepatitis B vaccination was 75%, higher than that of other vaccines, and the authors attributed this to considering of hepatitis B vaccination as a generally accepted routine practice and to the fact that patients had more knowledge about hepatitis B vaccination. Lower rates of hepatitis B vaccination in our study may be due to the fact that the patients avoided going out during the pandemic period and other vaccine recommendations such as COVID-19 and influenza, come to the fore during this period. In addition, 36.6% of our patients were immune due to natural hepatitis B infection. COVID-19 vaccination acceptability was 58.3% in Egyptian survey study among hemodialysis patients.[15] COVID-19 vaccination uptake was 77.5% in another study.[16] In our study, COVID-19 vaccination rate was 87.1%. The higher rate of COVID-19 vaccination compared with other vaccines in our study population can be attributed to getting more information about COVID-19 disease and COVID-19 vaccines via media, internet and healthcare workers and to the fear of COVID-19 infection which could be fatal outcomes.

In our study, the main reasons for not taking vaccination were lack of knowledge and misconceptions about vaccines; and the main sources of information about vaccination were health personnel. Similar to our study, in three previous studies, the main reason for not being vaccinated was the lack of knowledge.[9,13,14] Vaccination rates may be increased only by providing hemodialysis patients with detailed information. Similar to our study, in a previous study, the main source of information was health personnel.[13] The recommendations made by physicians (family physician or nephrologist) might be more effective.[13] So, according to these findings, the role of the health personnel, especially physicians, is important in increasing vaccination rates (i.e., in increasing primary prevention) in hemodialysis patients.[9,13] A health policy on this issue, a standardized vaccination practice in hemodialysis centers, education of health personnel and cooperation between family physician and nephrologist can contribute to increase vaccination rates.[13]

There are some limitations of our study. First, our study group consisted of a limited number of patients from two dialysis centers. Second, education levels of most of our patients (89.2%) were primary school or illiterate. So, the thoughts about vaccines, vaccination rates or sources of informations may be different in the patients groups with higher education level.

CONCLUSION

Our findings showed that the rates of influenza, pneumococcal and hepatitis B vaccination were below the targeted levels and the main reason for this was the lack of information about vaccination and the main source of information about vaccination was health personnel. Strategies to increase the vaccination rate, is important in reducing vaccine-preventable diseases in CKD patients. Further multi-center studies with larger populations are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of KTO Karatay University Faculty of Medicine Non-medicine and Non-medical Device Researches Ethics Committee (Date: 29.12.2022, Decision No: 2022/009).

Informed Consent: Written consent was obtained from the patients participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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Evaluation of pressure ulcer development and risk factors in COVID-19 patients followed in the ICU

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ABSTRACT

Aims: In this study it was aimed to evaluate the causes of pressure ulcer development in COVID-19 patients followed in the intensive care unit (ICU).

Methods: Demographic data, comorbidities, laboratory parameters, treatment modalities and mortality rates of the patients were reviewed retrospectively from hospital records. In addition, Acute Physiology and Chronic Health Assessment (APACHE II), Sequential Organ Failure Assessment (SOFA), and modified NUTRIC scores were calculated. Braden scale was used for pressure ulcer evaluation.

Results: Eighty COVID-19 patients were included in the study. Pressure ulcers (PU) were detected in 29 (36.25%) of the cases, and no pressure ulcer was detected in 51 (63.75%) cases. 54 (69.7%) of the patients were male, 26 (32.5%) were female, and the mean age was 69 (61-77). The cases were divided into two groups according to the development of pressure ulcers. The APACHE II score was 24 (17-29) in the PU group and 18 (12-23) in the non-PU group (p=0.01), the mNUTRIC score was 4 (3-5) in the PU group and 3 (2-4) in the non-PU group.) (p=0.023), the Braden scale calculated at admission to the ICU was 11(10-13) in the PU group and 14(12-15) (p<0.001) in the non-PU group. A Braden scale score of <13 was found to be 22 (75.9) in the PU group and 14 (27.5) in the non-PU group, and 36 (45) patients in total (p<0.001).

Conclusion: The Braden Scale can be used in COVID-19 patients, since they are first admitted to the ICU, both for scoring the wound and predicting the (making a) prognosis quickly.

Keywords: COVID-19, pressure ulcer, ICU, Braden scale, mortality

INTRODUCTION

The viral outbreak caused by the novel coronavirus SARS-CoV-2 is responsible for the ongoing coronavirus (COVID-19) pandemic.[1] 30% of patients infected with COVID-19 are treated in the intensive care unit (ICU) for acute respiratory distress syndrome (ARDS), which requires emergency respiratory and hemodynamic support.[2] The mortality rate in COVID-19 patients followed with invasive mechanical ventilator therapy in the ICU is between 40-60%.[3] In addition to high mortality rates, the average duration of treatment for COVID-19 patients treated in the ICU is 9 (6-13) days.[4] In addition to the long duration of treatment, inactivity due to long-term follow-up on mechanical ventilators, advanced age, presence of various comorbidities, intense cytokine storm due to the nature of COVID-19 disease, prone position and use of various devices, excessive sedation, conditions such as lack of care and hygiene before and after the intensive care unit, changing positions less frequently than necessary in the ICU, malnutrition and deterioration of tissue perfusion may cause the development of pressure ulcers.[5]

The development of pressure ulcers (PU) is multifactorial and can occur in any part of the body, including the face, that is under pressure and if adequate precautions are not taken.[6] The consequences of pressure-induced skin and soft tissue injury ranges from unfading erythema of intact skin to deep ulcers extending to the bone.[7]

For optimal management of patients with pressure ulcers, it is necessary to identify simple prognostic predictors that will enable timely decisions to be made and cooperation between physician and nursing care.[12] One

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of the candidates with predictive potential for PU is the Braden scale.[13] The Braden scale (BS) is a commonly used indicator to predict the future of PU and its relationship with mortality rates.[14]

Our aim in this study is to investigate the causes of pressure ulcer development and possible risk factors in COVID-19 patients followed in the intensive care unit. In addition, our hypothesis is to investigate whether the Braden score can be used in COVID-19 patients who develop pressure ulcers.

METHODS

The study was carried out with the permission of Dokuz Eylül University Non-interventional Researches Ethics Committee (Date:25.08.2021, Decision No:2021/24-02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Eighty patients who were diagnosed with polymerase chain reaction (PCR) test and admitted to the intensive care unit between April and October 2020 were included in the study. Patients younger than 18 years of age, those who were in the intensive care unit for less than 24 hours, and those with insufficient medical knowledge and anamnesis were excluded from the study. Pregnant and lactating patients were also excluded from the study. Demographic data, medical histories, comorbidities, laboratory parameters, major events and treatment modalities, nutritional status, respiratory support and method, and mortality rates were reviewed retrospectively from hospital records.

Disease severity within the first 24 hours after each patient's admission to the ICU was calculated according to the relevant scoring criteria of the Acute Physiology and Chronic Health Assessment (APACHE II) and Sequential Organ Failure Assessment (SOFA).[15,16] Nutritional risk for each patient was assessed at ICU admission using the mNUTRIC score. The score, calculated by subtracting IL-6 values, consisted of five variables: age, APACHE II score, and SOFA score at admission, patient comorbidity, and length of hospital stay before the intensive care unit.[17] It has been reported that a modified NUTRIC score of 5 and above indicates that the patient has a high risk in terms of nutrition.[17] PU is divided into 4 grades by the European Pressure Ulcer Advisory Panel (EPUAP).[18] These stages are important in the detection and treatment of ulcers.

Stage 1: There is a spotless rash in a localized area, usually over bony prominences.

Stage 2: A scaleless red-pink sore, partial thickness loss of dermis presenting as an open ulcer. Bullas may develop.

Stage 3: Full thickness tissue loss. Subcutaneous fat may be visible, but bones, tendons, or muscles are not exposed. Dead skin may be present but does not hide the depth of tissue loss.

Stage 4: There is full-thickness tissue loss with exposed bone, tendon, or muscle.

There may be abrasions or crusts in some parts of the wound.

The Braden scale values of the patients were obtained from the nursing care records included in the patient observations.

The Braden scale includes six risk factors: sensory perception, moisture, activity, mobility, nutrition, and irritation / friction. Except for friction and irritation, each variable is scored between 1-4.[19] The total score of the scale is obtained by calculating the sum of the scores obtained from each of the sub-dimensions of the scale. The total score of the scale is obtained by summing the scores obtained from each of the sub-dimensions of the scale. The total score varies between 6-23. As the scores obtained from the scale decrease, the risk of pressure ulcer development increases.

Individuals with a scale score of 9 and below are considered to be at very high risk for the development of pressure ulcers, those of 10-12 are considered to be high-risk, those of 13-14 are considered to be medium risk, those of 15-18 are considered to be at low risk, and those above 18 are considered to be at no risk.[20]

As recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Parenteral and Enteral Nutrition (ESPEN);[21,22] The daily caloric intake of the patients was planned as 14 kcal/kg/day for patients with a body mass index (BMI) above 30 kg/m², and as 25 kcal/kg/day for patients with a body mass index below 30 kg/m². From patient observations, the planned calories and the day the target calories were reached during the first 14 days were recorded. Inaddition, the diet of the patients, the reasons for the interruption, whether they received additional vitamin support or not were recorded.

Statistical Analysis and Calculations of Sample Size

To define the retrospective power of the observed effect based on the sample size, we performed a post-hoc power analysis using G*Power 3.1.9.7 software. Participants were divided into two groups: Pressure Ulcer (n=29) and No-Pressure Ulcer (n=51). We used an alpha (α) error probability rate of 0.05 with an 0.80 effect size, and the power (1- β error probability) was 0.924.

All continuous variables were presented as mean standard deviation [SD] or median (IQR), and categorical variables were presented as numbers and percentage (%). Descriptive statistics for all variables were calculated with Student's t-test, Mann Whitney U-Test 2 or Fisher's Exact Test. Multivariate logistic regression analysis was

performed to investigate pressure ulcer risk factors. A p value of <0.05 was considered statistically significant. SPSS 26.0 Statistical Package was used for all analyses.

RESULTS.

Of the 109 COVID-19 patients admitted to the intensive care unit, 80 patients were included in the study. Patient selection is shown in the flow-chart (**Figure 1**). While pressure ulcers were detected in 29 (36.25%) of the cases, no pressure ulcer was detected in 51 (63.75%) cases. 54 (69.7%) of the patients were male, 26 (32.5%) were female, and the mean age was 69 (61-77). Patients included in the study were divided into two groups (PU and non-PU) according to the development of pressure ulcers. The mean age of the PU group was 78 (71-84), and the non-PU group was 65 (59-70) years old (p<0.001) (**Table 1**).

When the cases are evaluated in terms of disease scores, nutrition and wound site scores; the APACHE II score was 24 (17-29) in the PU group and 18 (12-23) in the non-PU group (p=0.01), the mNUTRIC score was 4 (3-5) in the PU group and 3 (2-4) in the non-PU group (p=0.023), the Braden scale calculated at admission to ICU was 11(10-13) in the PU group and 14(12-15) (p<0.001) in the non-PU group and those with a Braden scale <13 were found to occur in 22 (75.9) patients in the PU group and 14 (27.5) patients in the non-PU group, and 36 (45) patients in total (p<0.001) (**Table 1**).

Table 1. Demographic data, comorbidities and clinical outcomes of the patients

	All Patients (n=80)	Pressure Ulcer (PU)		p Value
		PU (n=29)	Non-PU (n=51)	
Age	69 (61-77)	78 (71-84)	65 (59-71)	< 0.001
Gender male	54 (66.7)	19 (65.5)	35 (68.6)	0.81
BMI, kg/m²	27.0 (24.0-32.0)	25.0 (22.5-31.0)	27.0 (25.0-33.0)	0.07
APACHE II score	20 (14-27)	24 (17-29)	18 (12-23)	0.010
SOFA score*	8 (6-11)	8 (8-11)	8 (4-10)	0.10
GCS (admission to ICU)	13 (7-15)	10 (7-14)	15 (7-15)	0.08
NUTRIC score	3 (2-4)	4 (3-5)	3 (2-4)	0.023
Braden scale (admission to ICU)	13 (10-15)	11 (10-13)	14 (12-15)	< 0.001
Braden scale <13	36 (45)	22 (75.9)	14 (27.5)	< 0.001
Comorbidities	72 (90)	27 (93.1)	45 (88.2)	0.70
Hypertension	50 (61.7)	19 (65.5)	31 (60.8)	0.81
Diabetes Mellitus	32 (39.5)	14 (48.3)	18 (35.3)	0.34
COPD	16 (19.8)	5 (17.2)	11 (21.6)	0.78
Congestive Heart Failure	13 (16.0)	6 (20.7)	7 (13.7)	0.53
Chronic Liver Failure	13 (16.0)	5 (17.2)	8 (15.7)	1.00
Atrial Fibrillation	11 (13.6)	7 (24.1)	4 (7.8)	0.09
Chronic Renal Failure	9 (11.1)	3 (10.3)	6 (11.8)	1.00
Cerebrovascular Disease	8 (9.9)	2 (6.9)	6 (11.8)	0.70
Malignancy	8 (9.9)	7 (24.1)	1 (2.0)	0.003
Dementia	6 (7.4)	5 (17.2)	1 (2.0)	0.022
Parkinson's Disease	2 (2.5)	1 (3.4)	1 (2.0)	1.00
Duration of Stay (days)				
Hospital Stay	17 (10-24)	16 (8-26)	17 (10-23)	0.78
ICU Stay	10 (5-14)	8 (3-14)	10 (6-14)	0.19
Pressure Ulcer Features				
Location				
Sakral	22 (27.5)	22 (75.9)	N/A	N/A
Gluteal	4 (5.0)	4 (13.8)	N/A	N/A
Back	1 (1.3)	1 (3.4)	N/A	N/A
Other	2 (2.5)	2 (6.9)	N/A	N/A
Stage				
Stage I	23 (28.8)	23 (79.3)	N/A	N/A
Stage II	5 (6.3)	5 (17.2)	N/A	N/A
Stage III	1 (1.3)	1 (3.4)	N/A	N/A
Measure				
Size ≤ 5 cm²	7 (8.8)	7 (24.1)	N/A	N/A
5 cm² <Dimension≤ 10 cm²	14 (17.5)	14 (48.3)	N/A	N/A
10 cm² <Dimension ≤ 15 cm²	6 (7.5)	6 (20.7)	N/A	N/A
Size > 15 cm²	2 (2.5)	2 (6.9)	N/A	N/A
Mortality				
Hospital	58 (71.6)	25 (86.2)	33 (64.7)	0.042
ICU	56 (69.1)	24 (82.8)	32 (62.7)	0.08

All values were expressed as n (%) or median (IQR). PU: Pressure Ulcer; BMI: Body Mass Index; APACHE II Score: Acute Physiology and Chronic Health Assessment Score; SOFA Score: Sequential Organ Failure Assessment Score; GCS: Glasgow Coma Scale; NUTRIC Score: Critical Patient Nutritional Risk Score; COPD: Chronic Obstructive Pulmonary Disease; N/A, Not Valid; ICU: Intensive Care Unit., *Calculated on the Day of Admission to the ICU.

When evaluated in terms of laboratory data the statistical significance was determined as follows ; hemoglobin (g/dL) was 11.3 (9.7-13.2) in the PU group and 12.8 (11.5-14) in the non-PU group (p=0.006), BUN (mg/dL) was 52 (29.5-92) in the PU group and in the non-PU group 27 (21-43) (p<0.001) in the group, creatinine (mg/dL) was 1.81 (0.83-3.61) in the PU group, and 0.85 (0.75-1.41) (p=0.016) in the non-PU group, HS troponin I (ng/mL) 64 (14-503) in the PU group and 18 (11-59) in the non-PU group (p=0.004), D-dimer (µg/mL) 3.60 (1.91-5.82) in the PU group and 3.60 (1.91-5.82) in the non-PU group 1.10 (0.80-2.50) (p<0.001) and procalcitonin (ng/mL) in the PU group 1.29 (0.33-4.01) in the PU group and 0.27 (0.11-0.87) in the non-PU group (p<0.001) (Table 2).

When the nutritional status of the patients is evaluated; target calories were calculated as 1350 (1270-1475) in the PU group and 1420 (1330-1530) in the non-PU group (p=0.048). In terms of reaching the target calories, on the 1st day of admission to the ICU, it was 800 (425-1200) in the PU group, 1200 (800-1400) (p=0.024) in the non-PU group, and in the 5th, day was 1200 (960-1440) in the PU group, 1400 (1200-1500) (p=0.025) in the non-PU group, and were found to be statistically significant (Table 3). When multivariate regression analysis of independent risk factors related to pressure ulcer developing in COVID-19 patients followed in the ICU was performed; Braden scale to be <12 7.60 (1.94-29.75) (p=0.004) and D-dimer to be >1.72 µg/mL 6.59 (1.66-26.20) (p=0.007) OR (95% CI) were found to be statistically significant (Table 4).

Table 4. Analysis of independent risk factors for pressure ulcers in critically ill patients with COVID-19

	OR (95% CI)	p Value
Braden scale ≤12	7.60 (1.94-29.75)	0.004
APACHE II score	1.04 (0.97-1.13)	0.28
D-dimer> 1.72 µg/Ml	6.59 (1.66-26.20)	0.007
Malignancy	11.72 (0.99-138.99)	0.05
Flux	3.71 (0.94-14.73)	0.06
Supplemental protein supplement	0.39 (0.06-2.44)	0.32

OR, odds ratio; CI, confidence interval;

Table 2. Laboratory data of the patients on the day of admission to the intensive care unit

Laboratory Values*	All Patients (n=80)	Pressure Ulcer (PU)		p Value
		PU (n=29)	Non-PU (n=51)	
WBC, ×10³/µL	11.95 (9.28-16.10)	14.10 (10.10-18.95)	11.70 (8.90-15.60)	0.28
Neutrophil ×10³/µL	9.60 (8.20-13.68)	10.80 (7.70-14.40)	9.45 (8.20-13.10)	0.66
Hemoglobin, g/dL	12.4 (10.9-13.5)	11.3 (9.7-13.2)	12.8 (11.5-14.0)	0.006
Lymphocyte ×10³/µL	0.5 (0.3-0.8)	0.5 (0.3-1.0)	0.5 (0.4-0.7)	0.59
Platelet, ×10³/µL	271.0 (200.5-372.5)	288.0 (190.5-370.5)	268.0 (211.0-385.0)	0.60
BUN, mg/dL	33.0 (23.3-58.0)	52.0 (29.5-92.0)	27.0 (21.0-43.0)	< 0.001
Creatinine, mg/dL	1.00 (0.75-2.03)	1.81 (0.83-3.61)	0.85 (0.75-1.41)	0.016
Total Bilirubin, mg/dL	0.90 (0.62-1.10)	0.83 (0.58-1.07)	0.91 (0.64-1.10)	0.68
CRP, mg/L	150.5 (74.3-202.3)	157.0 (97.0-233.5)	147.0 (71.0-197.0)	0.44
AST, U/L	48 (33-75)	42 (31-96)	49 (34-73)	0.77
LOWER, U/L	33 (23-65)	30 (19-66)	36 (24-64)	0.28
LDH, U/L	564 (406-710)	570 (312-675)	559 (450-742)	0.53
Albumin, g/dL	3.06 (2.72-3.23)	3.00 (2.53-3.19)	3.07 (2.80-3.28)	0.11
Ferritin, ng/mL	463 (301-924)	426 (261-737)	554 (332-1124)	0.12
HS Troponin I, ng/L	25 (11-86)	64 (14-503)	18 (11-59)	0.004
D-Dimer, µg/mL	1.72 (0.94-4.40)	3.60 (1.91-5.82)	1.10 (0.80-2.50)	< 0.001
D-Dimer> 1.72 µg/mL	40 (50)	23 (79.3)	17 (33.3)	< 0.001
Procalcitonin, ng/mL	0.52 (0.15-2.39)	1.29 (0.33-4.01)	0.27 (0.11-0.87)	0.007

All values were expressed as n (%) or median (IQR). PU: Pressure Ulcer; WBC:Leukocyte; BUN, Blood Urea Nitrogen; CRP, C-Reactive Protein; AST: Aspartate Transaminase; ALT: Alanine Transaminase; LDH: Lactate Dehydrogenase; HS Troponin I: High Sensitivity troponin I. *Calculated on the day of admission to ICU.

Tablo 3. Major events and treatment modalities

	All Patients (n=80)	Pressure Ulcer		p value
		PU (n=29)	Non-PU (n=)	
Respiratory support time				
HFNO, days	1 (0-3)	0 (0-2)	2 (0-4)	0.015
NIMV, days	0 (0-1)	0 (0-2)	0 (0-1)	0.67
IMV, days	3 (0-10)	3 (1-12)	3 (0-9)	0.35
Termination of respiratory support	60 (75.0)	24 (82.8)	36 (70.6)	0.17
Treatment modalities				
FLUX	36 (45.0)	19 (65.5)	17 (33.3)	0.010
RRT	24 (30.0)	11 (37.9)	13 (25.5)	0.31
Sedation	60 (75.0)	24 (82.8)	36 (70.6)	0.29
Vasopressor need	58 (72.5)	24 (82.8)	34 (66.7)	0.11
Corticosteroid therapy	68 (85.0)	22 (75.9)	46 (90.2)	0.11
Pulse corticosteroid therapy	32 (40.0)	7 (24.1)	25 (49.0)	0.035
Tocilizumab	7 (8.8)	0 (0.0)	7 (13.7)	0.045
Tracheostomy	1 (1.3)	1 (3.4)	0 (0.0)	0.36
Prone position	38 (47.5)	7 (24.1)	31 (60.8)	0.002
Nutritional properties				
Nutritional route, enteral	80 (100.0)	29 (100.0)	51 (100.0)	N/A
Additional protein support	22 (27.5)	2 (6.9)	20 (39.2)	0.002
Additional vitamin support	70 (87.5)	24 (82.8)	46 (90.2)	0.48
Target calories, kcal	1400 (1300-1520)	1350 (1270-1475)	1420 (1330-1530)	0.048
Continuation and Cessation of Feeding				
Planned	16 (20.0)	7 (24.1)	9 (17.6)	0.57
Vomiting	9 (11.3)	6 (20.7)	3 (5.9)	0.07
Bleeding	7 (8.8)	4 (13.8)	3 (5.9)	0.25
Abdominal distention	3 (3.8)	1 (3.4)	2 (3.9)	1.00
to continue uninterrupted	50 (62.5)	14 (48.3)	36 (70.6)	0.06
Nutritional support, kcal				
1st day of admission to ICU	1200 (600-1375)	800 (425-1200)	1200 (800-1400)	0.024
2nd day of admission to ICU	1300 (1000-1485)	1200 (875-1400)	1400 (1200-1500)	0.003
3rd day of admission to ICU	1400 (1150-1500)	1300 (980-1440)	1400 (1200-1500)	0.05
4th day of admission to ICU	1400 (1100-1500)	1300 (960-1440)	1400 (1225-1500)	0.18
5th day of admission to ICU	1400 (1000-1500)	1200 (960-1440)	1400 (1200-1500)	0.025
7th day of admission to ICU	1400 (1000-1440)	1250 (960-1440)	1400 (1200-1500)	0.31
10th day of admission to ICU	1400 (1000-1440)	1200 (1000-1400)	1400 (1000-1500)	0.07
14th day of admission to ICU	1200 (1000-1430)	1000 (1000-1500)	1200 (800-1420)	0.77
The number of the days achieved the target calorie	2 (2-3)	3 (2-3)	2 (2-3)	0.56

All values are expressed as n (%) or median (IQR). PU: Pressure Ulcer; HFNO, High-flow nasal oxygen; NIMV, Non-invasive mechanical ventilation; IMV, Invasive mechanical ventilation; AKI, Acute Kidney Injury; RRT, Renal Replacement Therapy; N/A, not valid; ICU: Intensive Care Unit

DISCUSSION

In this study, pressure ulcers were detected in 29 (36.25%) of 80 critically ill patients with COVID-19 treated in the ICU, and the mean age of this group was found to be high (78 years old) (71-84). In the PU group, while the mNUTRIC score of 4 (3-5) and the APACHE II score of 24 (17-29) in the first 24 hours were high, the Braden score 12 (11-13) was low. When the independent risk factors for the development of PU were analyzed, it was found statistically significant that the Braden score was <12 and the D-dimer value was >1.72 µg/ml.

In two different studies conducted in Turkey, in-hospital PU rates were found to be 5.8% and 10.4%.[8] Pressure ulcers are one of the common complications of hospital care, and their incidence rates in intensive care patients varies between 1.6% and 26.8% in prevalence studies.[9]

This situation, which has a high incidence, may contribute negatively to the existing morbidity and high mortality rates, especially in COVID-19 patients followed in the ICU. In addition, PU, which is completely preventable with appropriate measures, is difficult to treat and is a serious financial burden in the healthcare system.[10] Gencer et al.[11] reported in a study they conducted that PU may develop in 308,796 patients annually in our country and the annual care cost of these patients may be 1 billion 425 million dollars.

There are publications implies that advanced age and male gender are important risk factors for the development of PU.[23] Patients over the age of 60 are prone to develop pressure injuries due to decreased skin elasticity, insufficient hydration, and changes in sensitivity.[24] In a study conducted by Kurtulus et al.[25] it was determined that the development of pressure injuries was higher in male patients aged 65 and over, but this result was not statistically significant. Similarly, the mean age of the PU group was found to be statistically significantly higher in our study; however, being male was not found to be statistically significant, although PU was more common in male gender as clinical observation.

In a meta-analysis study, which researching COVID-19 patients treated in the ICU and their risk factors, the mortality rate was found to be 41.6%, while in our study the mortality rate was found to be 62.7%.[26] The fact that patients admitted to the ICU are critically ill is consistent with high APACHE II and mNUTRIC scores and low BS, as we found in our study. Previous studies which conducted in different populations, it was found that a BS ≤15 may be associated with short-term mortality.[14]

In another cohort study of COVID-19 in the literature, lower BS at admission was found to be consistent with increased in-hospital mortality.[27] In the independent risk analysis for PU in our study, BS <12 was found to be statistically significant (p <0.004). According to the results of the current study, it has been proven that BS can be used as a mortality predictor as well as being a simple, rapid and bedside nursing assessment tool that can evaluate skin integrity.[27]

Risk factors for PU includes cerebrovascular disease, cardiovascular disease, recent lower extremity fractures, incontinence, and diabetes.[28] However, it is not clear whether these are independent risk factors or merely reflect the high prevalence of inactivity in fragile, older adult patients.[28]

In our study, the presence of malignancy and dementia, which are among the comorbidities, were prominent. It can be thought that the common point may be nutritional deficit, insufficient self-care and inactivity. Immobility is the most important host factor contributing to the development of pressure-related skin and soft tissue injury.[29] Immobility may be an important problem in COVID-19 patients followed in the ICU, especially in patients who are oversedated and followed up on mechanical ventilators. Unfortunately, it is not easy to measure the level of inactivity clinically.[29] The best solution for inactivity due to the existing comorbid disease or the treatment modalities applied is an effective physiotherapy and staff-nurse active cooperation with position change in a short time.[29]

A hemoglobin level below 12 g/dl, which is among the risk factors, increases the risk of pressure ulcers by decreasing the tissue resistance and O_2 carrying capacity of the blood.[30] In our study, in accordance with the literature, mean hemoglobin levels were found to be low in the PU group. Since anemia impairs tissue resistance and nutrition, it affects injury negatively.[30] In the independent risk analysis for PU formation, a D-dimer level of >1.72 µg/ml showed that COVID-19 disease is a prothrombotic disease.[31] In a systematic review, vascular endothelial abnormalities, disruption of the coagulation cascade, thromboembolic events, tissue circulation, and decreased oxygen delivery have been found.[31] This situation explains the D-dimer elevation in patients with PU. Corticosteroids were thought to have a role in the treatment of COVID-19 patients with elevated inflammatory parameters, and it was one of the first drugs that were shown to reduce mortality as a result of studies.[32]

In our study, it was found that the use of pulse corticosteroid and tocilizumab was high in the group without PU. This shows that COVID-19 is at the

forefront in the treatment of patients in the non-PU group and that secondary infection does not develop. Since the septic process did not develop in patients who did not develop secondary infection, tissue circulation did not deteriorate, and PU did not develop.[33] Nutritional deficiency is one of the important factors affecting the development of PU.[34]

In severe infections such as COVID-19, cytokine storm induces hypercatabolism, secondary hypermetabolism and insufficient energy intake cause delay in wound healing.[34] The American National Pressure Ulcer Long-Term Care Working Group (NUPAP) defined inadequate diet and malnutrition as risk factors for PU.[30] Berlowitz et al.[31] identified pre-existing malnutrition and/or weight loss as a positive predictive variable for PU. Similarly, in our study, it was determined that the targeted calorie amount in the PU group was lower than the group without PU, but despite this the targeted calorie amount in the PU group could not be reached. This situation can be explained by the calculation of the target calorie, which calculated as 25 kcal/kg/day in accordance with the ESPEN recommendations,[22] and as the lower amounts due to the lower average BMI in the PU group. In the group that did not develop pressure ulcers, the target calories were reached. It has also been determined that additional protein supplementation contributes to the prevention of pressure ulcer development. Protein loss causes negative nitrogen balance, and the risk of pressure injury increases with subcutaneous tissue loss.[34] In our study, the percentage of following the prone position was higher in the group without PU. In the patients followed in the prone position, simple mild abrasions and erythema that did not require treatment were found on the face, but lesions that did not reach the size to be included in any grading. However, no pressure ulcers were observed. Although severe ARDS patients due to COVID-19 were followed in the prone position for 12-16 hours, as suggested by the relevant guidelines, PU related with this position was not observed.[35]

Limitations

We could not use any anthropometric measurements for nutritional assessment in this study because these data were not available in our medical records. Secondly, 80 patients who met the inclusion criteria were included, and studies with larger sample sizes may be useful in this regard. In our study, although independent risk factor analysis was performed, root analysis was not performed for pressure ulcers. Doing so could help us better understand the causes of pressure ulcer development. Finally, randomized and controlled studies are needed because of the limitations inherent in retrospective observational studies.

CONCLUSION

There are many factors that affect the development of pressure ulcers in COVID-19 patients followed in the intensive care unit. Pressure ulcers can cause serious morbidity and mortality. This situation, which has a serious financial burden, can be prevented with effective follow-up and treatment. We think that the Braden Scale should be followed by doctors as well as a nurse follow-up tool, since it predicts both the wound score and prognosis of COVID-19 patients from the first admission to the ICU.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dokuz Eylül University Non-interventional Researches Ethics Committee (Date:25.08.2021, Decision No:2021/24-02).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Distribution of yeasts in fungal urinary tract infections from a tertiary care hospital

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ABSTRACT

Aims: Urinary tract infections caused by fungi in critically ill patients steadily increasing in recent years. Fungiuria is a marker of contamination, colonization, or infection in the lower or upper urinary tract. As urinary catheters especially long-term usage was the most important risk factor for fungiuria. The identification of yeast isolates at the species level is crucial for the appropriate management of infection. We conducted this study to describe the epidemiological features of fungiuria in patients.

Methods: The yeast species were identified by using conventional methods and automated systems. Demographic data were recorded from the electronic medical records.

Results: *Candida albicans*, were predominant compared to non-*albicans Candida* species and yeast-like fungi. Among non-*albicans Candida*, the most common species were *Candida tropicalis* followed by *Candida glabrata* complex. Fungiuria was more common in females than in males. Underlying conditions were present in patients the most common risk factors were antibiotic therapy before the detection of yeasts and using a urinary catheter.

Conclusion: Epidemiological data and antimicrobial therapy play an important role in the treatment of urinary tract infections. For this reason, the identification of fungi at the species level is critical to assist the decision on antifungal therapy in complex cases. In all patients with fungal growth in urine culture, the underlying risk factors should be evaluated first. Depending on the correction of risk factors, fungiuria may resolve spontaneously. This is seen as the best approach both to reduce treatment costs and to prevent resistance to antifungals.

Keywords: Fungiuria, candiduria, urinary tract infection, urinary catheter

INTRODUCTION

Fungi and bacteria may be etiological agents in urinary tract infections (UTIs). UTIs caused by fungi in critically ill patients steadily increasing in recent years. Especially, *Candida* species important opportunistic pathogen causing UTIs.[1,2]

Candiduria (i.e., the presence of *Candida* species in urine) is a marker of contamination, colonization, or infection in the lower or upper urinary tract. There are no reference standards available for the definitive diagnosis tests to distinguish infection from colonization in urine samples.[3] Patients with candiduria can be categorized as asymptomatic or symptomatic according to diagnostic criteria.[4]

Generally, candiduria is typically rare and asymptomatic in healthy patients.[5-7] Antifungal therapy is generally not recommended in asymptomatic patients. Infectious Diseases Society of America (IDSA) strongly recommends correcting the underlying risk factors, removing or replacing the catheter in patients with urinary catheters is sufficient to prevent infection.[4,8-10]

Use of catheter, broad-spectrum antibiotic therapy, prolonged hospitalization, long duration in intensive care units (ICU), diabetes mellitus, renal disease, coronary heart disease, liver disease, prematurity, total parenteral nutrition and urinary tract malformation, immunocompromised patients are presented as more important risk factors for fungal UTI.[2,11,12] As urinary catheter especially long-term usage was believed to be the most important risk factor for candiduria.[2,8,13]

Although *Candida albicans* is the most frequently reported species in fungal urinary tract infection, non-*albicans Candida* (NAC) species (i.e. *Candida tropicalis*,

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Candida glabrata complex, *Candida parapsilosis* complex, *Candida lusitaniae*, *Candida guilliermondii*, and *Candida krusei*) are also increasing now as the causative agent of UTI. The important factor about NAC species is that they are more difficult to treat. Many strains of NAC are resistant to antifungals (i.e., many *C. glabrata* complex isolates (acquired) and all *C. krusei* isolates (adaptive) are resistant to fluconazole. Therefore, the identification of yeast isolates at the species level is crucial for the appropriate management of infection.[2,14,15]

It is important to decide in the case of candiduria whether it is colonization or an infection that requires treatment because candiduria is usually accepted as colonization or contamination by most physicians, but it may be the only sign of invasive candidiasis.[7,11,16]

At our hospital, fungal UTIs are caused by yeast such as *Candida* species and yeast-like fungi such as *Trichosporon* species. As far as we know studies on the epidemiology and prognostic value of fungiuria are not very common. Therefore, we conducted this study to describe the epidemiological features of fungiuria in patients. We aimed to evaluate the prevalence of fungi (yeast and yeast-like fungi) that cause urinary tract infections in inpatients and outpatients during a 3 years study period. In this way, we suppose that we will contribute to surveillance studies in our province, our country and perhaps globally.

METHODS

The study was carried out with the permission of Eskişehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (Date: 26.10.2021, Decision No: 10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, we evaluated the results of all urine samples taken from the patients who applied to our laboratory with a preliminary diagnosis of urinary tract infection for three years (2019-2021).

The urine samples were collected and stored in a disposable sterile bottle with a screw lid. Before sample collection, patients were instructed on how to collect mid-stream urine.[17] All urine samples received from one patient were considered as a single sample. Although urine culture is regarded as the gold standard for the detection and identification of fungi, microscopic examination of urine is a useful tool for diagnosing fungal UTI.[18] Microscopy of yeast in the urine such as budding cells, ovoid- shaped yeast cells, hyphal element (pseudohyphae) and arthroconidia is the first clue to the presence of a fungal infection.[19]

Urine specimens were inoculated on blood agar (RTA, Turkiye), Eosin Methylen-blue (EMB) agar (RTA, Turkiye) and Sabouraud's dextrose agar (SDA) (RTA, Turkiye) with a calibrated loop technique delivering 0.001 ml of urine as per standard protocol for urine culture. The culture plates were incubated aerobically at 35°C for 24-48 h. The yeast species were identified by using of tests including Gram's staining, germ tube test, chlamydospore formation on corn meal agar (RTA, Turkiye), color appearance on CaandidaCHROM agar (RTA, Turkiye) and VITEK 2 Compact (bioMérieux, Marcy l'Etoile, France) identification system which is YST card was used for yeast and yeast-like fungi (YLF).

Demographic data including age, gender, comorbidities, cause of admission (medical or surgical) and the underlying malignancy were recorded from the electronic medical records. Likewise, previous antibiotic use and urinary catheter insertion were recorded from electronic medical records.

RESULTS

During the study period, we received 61843 urine samples from different polyclinics, wards, and ICUs of our tertiary city hospital. 10187 (16.47%) were found positive; among them, 9009 (88.44%) and 1178 (11.56%) had bacteriuria and fungiuria, respectively. Regarding the urine culture results of our patients, growth was not detected in 46073 (74.5%) of the patients and contamination was detected in 5583 (9.03%).

In total, 1183 strains of yeasts isolates were recovered from the 1178 patients with fungiuria. The distribution of species is shown in **Table 1**. *C. albicans* (n=557 47.1%), were predominant compared to NAC species and YLF. The incidence rate of yeasts was determined as *C. tropicalis* (n=230 19.4%), *C. glabrata* complex (n=133 11.2%), *Trichosporon asahii* (n=70 5.9%), *C. parapsilosis* complex (n=41 3.5%), *Candida kefyr* (n=41 3.5%). *C. lusitaniae* (n=22 1.9%), *C. krusei* (n=18 1.5%), *Candida famata* (n=16 1.4%), *Trichosporon mucoides* (n=12 1.0%) and other *Candida* species (n=43 3.6%).

In our study, NAC species were isolated in 46.0% and YLF were isolated in 6.9%. Among NAC, the most common species were *C. tropicalis* followed by *C. glabrata* complex. Among YLF, the most common species were *T. asahii* (5.9%) followed by *T. mucoides* (1.0%).

Mixed infections with two microorganisms were found in thirty-five cultures (3.0%), thirty (2.6%) together with bacteria and five (0.4%) with two different yeasts (**Table 2**).

Table 1. Percentage of distribution of urinary isolates of fungi species

Species	No	%
Candida albicans	557	47.1
Candida tropicalis	230	19.4
Candida glabrata complex	133	11.2
Candida kefyr	41	3.5
Candida parapsilosis complex	41	3.5
Candida lusitaniae	22	1.9
Candida krusei	18	1.5
Candida famata	16	1.4
Other *Candida* Species*	43	3.6
**Candida guilliermondii*	9	20.9
**Candida ciferrii*	9	20.9
**Candida dubliniensis*	6	14.0
**Candida melibiosica*	5	11.6
**Candida lambica*	4	9.3
**Candida sphaerica*	4	9.3
**Candida pelliculosa*	2	4.7
**Candida rugosa*	2	4.7
**Candida norvegensis*	1	2.3
**Candida utilis*	1	2.3
Trichosporon asahii	70	5.9
Trichosporon mucoides	12	1.0
Total	1183	100.0

Table 2. Mixed infections of yeasts and bacteria found in urine with fungiuria

Mixed infections	number	%
With bacteria	30	85.7
Candida albicans+*Enterococcus faecium*	17	48.6
Candida albicans+*Enterococcus faecalis*	1	2.9
Candida albicans+*Staphylococcus hominis*	1	2.9
Candida albicans+*Escherichia coli*	1	2.9
Candida albicans+*Klebsiella pneumoniae*	1	2.9
Candida albicans+*Pseudomonas aeruginosa*	1	2.9
Candida tropicalis+ *Enterococcus faecium*	1	2.9
Candida tropicalis+*Enterococcus faecalis*	2	5.7
Candida tropicalis+*Morganella morganii*	1	2.9
Candida tropicalis+*Staphylococcus hominis*	1	2.9
Candida glabrata complex+*Enterococcus faecalis*	1	2.9
Candida glabrata complex+*Acinetobacter baumannii*	1	2.9
Candida glabrata complex+*Klebsiella pneumoniae*	1	2.9
With two yeasts	5	14.3
Candida albicans+*Trichosporon asahii*	3	8.6
Candida albicans+*Candida glabrata* complex	1	2.9
Candida tropicalis+*Candida kefyr*	1	2.9
Total	35	100.0

Out of these 1178 fungiuria cases, 793 (67.3%) patients were from ICU, 292 (24.8%) were from wards and 93 (7.9%) were from polyclinics. *C. albicans* was the most frequently isolated species from the samples of patients in the ICUs (365/793 46.0%) and in the wards (132/292 45.2%).

In this study, fungiuria was more common in females 660 (56%), than in males 518 (44%). Out of 1178 isolates, 93 (7.9%) were from outpatients and 1085 (92.1%) were isolated from inpatients.

The mean age of presentation of the patients was 68.34±17.69 years (range 0-96 years). Age group analysis showed that 31 (2.6%) patients were under 16 years old, 32 (2.7%) were between 16 and 30 years, 125 (10.6%) were between 31 and 55 years, 496 (42.1%) were between 56 and 75 years, and 494 (41.9%) were older than 76 years (Table 3). The highest isolation rates of yeast were found in an age group above 55 years.

Table 3. Age and sex distribution pattern of fungi species from urine samples (n=1178)

Age	Male	Female	No %
<15	13	13	26 (2.2)
16-30	5	32	37 (3.1)
31-55	42	83	125 (10.6)
56-75	240	256	496 (42.1)
>76	218	276	494 (41.9)
Total	518 (44%)	660 (56%)	1178 (100%)

Less than half of the patients (445/1178 37.8%) had comorbidities, the most common of which were diabetes mellitus 7.81% (n=92), lung diseases 7.30% (n=86), hypertension 4.75% (n=56), malignant neoplasm 4,41% (n=52), vascular and heart diseases 4.16% (n=49), kidney diseases 3.99% (n=47), cerebrovascular diseases 2.29% (n=25) and immunodeficiency 1.1% (n=13). Ten patients had kidney stones, nine patients had urinary tract anomalies, three patients had cirrhosis and three patients had vaginitis. Our study showed that candiduria is common in patients with diabetes mellitus.

Underlying conditions were present in patients the most common risk factors were antibiotic therapy (998/1178 84.7%) before the detection of yeasts and using a urinary catheter (860/1178 73%). Of the patients using urinary catheters, 86.6% (n=745) were hospitalized in the intensive care unit and 13.4% (n=115) were hospitalized in wards.

DISCUSSION

Epidemiological data and empirical antimicrobial therapy play an important role in the treatment of urinary tract infections, which cause a significant burden worldwide. For this reason, the identification of fungi at the species level is critical to assist the decision on antifungal therapy in complex cases.[20] Our study characterizes a single-center experience on fungiuria over three years. The presence of a wide variety of fungi (yeasts and YLF) in the urine is known as fungiuria. The presence of *C. albicans* and NAC species in the urine is known as candiduria.[7]

Even though NAC species now account for a significant proportion of clinical isolates collected worldwide in hospitals. *C. albicans* is the most common cause of nosocomial fungal urinary tract infections. Regarding the high resistance to some antifungal agents of NAC species such as *C. glabrata* complex and *C. krusei*, the detection of NAC species in patients' urine samples should be important for the treatment.[21]

Contamination is common in patients who do not follow clean urine specimen collection guidelines. A new urine sample is recommended to exclude contamination. If the new specimen yields no yeasts, there is no need to continue studies for diagnosis.[22]

Fungus is considered to be the second leading pathogen causing UTI in ICUs after *Escherichia coli*.[23] Fungal UTIs encompass a broad variety of fungi. The overwhelming majority of UTIs are caused by *Candida* spp. but yeast-like species are also prevalent such as *Trichosporon* spp.[19]

The *C. albicans* was the most important yeast associated with human candiduria in the last decades.[21] The reported incidence of candiduria varies (10-68.42%) in different geographical locations. In the literature, *C. albicans* growth was reported to vary widely.[8,10,11,13,14,20,24-27]

In the present study, the frequency of *C. albicans* (47.1%) was higher than NAC species (46.0%) and yeast-like species (6.9%). Among NAC species, *C. tropiclis* (19.4%) followed by *C. glabrata* complex (11.2%) had the highest frequency compatible with the literature.[2,28] Contrary to a study by Paul et al.[29] and Kobayashi et al.[10] according to our study *C. albicans* is the most common species of fungiuria. Similar to some previous studies, we found that *C. tropicalis* was the most common of the non-*albicans* species isolated.[2,21,25] It was reported as *C. tropicalis* (22.2%) was the most common of the non-*albicans* species isolated and non-*albicans* yeasts were found at 42.2% in another similar study.[10] Nevertheless, our data was found to differ from the data presented by Singla et al.[30] and Pramodhini et al.[25] They reported that *C. tropicalis* has been frequently (first leading agent) identified in 57.3% and 65.7% of patients with candiduria respectively. Although lower than the results of the two researchers, Paul et al.[29] found that *C. tropicalis* was the most frequently isolated microorganism from candiduric patients with an incidence rate of 30.5%, followed by *C. albicans*.[3]

Although in our study and some previous studies *C. glabrata* complex was found to be the third leading agent of candiduria, generally the incidence of *C. glabrata* complex isolated from urine is increasing throughout the world.[6,13,15,17,31,32] There is a consensus in some studies that the high prevalence of NAC species, especially *C. glabrata* complex, increases in diabetic patients.[17,31] *C. parapsilosis* complex uncommon in urine and frequently significantly lower than the *C. trpicalis* and *C. glabrata* complex in our study. This result is also compatible with the literature.[6,7,15] Our opinion associated this with the low number of neonates and pediatric patients in our study.

In the present study, *T. asahii* is the most prevalent species among the yeast-like strains isolated from urine samples. However, in contrast with that Gharaghani et al.[3] reports showed *Trichosporon* species was more commonly isolated from the urine samples but our study similar to Francisco et al.[19]

In our study, we detected *Candida* species simultaneously with another urinary tract pathogens (yeast-bacteria) or two different yeast species (yeast-yeast) in the same urine samples.

In total, five patients had mixed infections caused by two different yeast and 30 patients had mixed infections caused by bacteria (**Table 2**). Mixed infections of yeasts and bacteria were found in the urine with fungiuria; the *C. albicans* 4.7% co-isolated with other species, *C. glabrata* complex 2.7% co-isolated with other species and *C. trpicalis* 2.6% co-isolated with other species. Gharaghani et al.[21] found similar results in their study.

In some studies, the frequency of yeast-yeast or yeast-bacteria co-isolation in candiduria cases has been reported as (3.5-10%).[1,3,11,12,26,33] The data obtained from our study revealed that 3.0% of candiduria patients can harbor two or more species at the same time. According to the results of many studies, our finding was found to be low.[11]

The incidence of candiduria in our hospital was most common in patients admitted to ICUs (67.3%). Similarly, according to different studies, the most important predisposing factors in creating candiduria were hospitalization in ICUs.[12,14] We think that this may be related to the prolonged stay in the ICU, the increase in the number of interventional procedures and the long-term use of empirical antibiotics.

In our study the female:male ratio (1.3:1) was observed similar to the female dominance in previous studies. Since *Candida* species are an important part of the normal microbial flora in the vagina, many researchers associate the high frequency of candiduria in women with vulvovestibular colonization and vaginal candidiasis.[34] Three of the women (3/660 0.45%) had vulvovaginal candidiasis in our study. Many researchers associate, women are more often affected due to their shorter urethra.[3,6,10,13,17,25,26,31] Several studies have shown male predominance in the incidence of candiduria which are in disagreement with our study.[3,8,14,35]

The incidence of candiduria may vary according to age groups. According to previous studies, the incidence of candiduria was significantly increased when compared with the overall incidence in patients over 60 years of age and under 1 year of age.[25]

In our study, the majority of patients identified with fungiuria were in the age group of 56 to 75 years (42.1%), followed by the 76 to 96 age group (41.9%). Our study has shown a high prevalence rate of UTIs in elderly people, which is concordant with other studies. Similar to many studies, in our study we noted the most common risk factors for fungiuria: age older than 55 years, female sex, diabetes mellitus, use prior antibiotics, catheter and ICU stay.[15]

We found several risk factors, diabetes in 7.81%, lung diseases in 7.30%, hypertension in 4.75%, malignant neoplasm in 4.41%, vascular and heart diseases in 4.16%, kidney diseases in 3.99%, cerebrovascular diseases in 2.29% and immunodeficiency in 1.1%. Diabetes mellitus was the most common underlying disease seen in the patients. It was found to be similar to previous studies.[15,33]

Once the presence of *Candida* in the urine is confirmed careful clinical evaluation should be performed to detect symptoms, diabetes mellitus, genitourinary structural abnormalities, decreased renal function and metabolic syndromes.[18] Patients with diabetes are at increased risk for candiduria, glycosuria and acidic pH can be due to an increased susceptibility to *Candida* colonization rates.[13,31] In conditions of immune deficiency, the commensal fungal microorganisms may convert into opportunistic pathogenic microorganisms, creating fungal UTIs.[34]

In many studies, it is stated that candidemia develops with candiduria in the presence of obstruction or urinary tract instrumentation, however in a low percentage.[17] Candidemia was not observed in any of the patients included in our study.

Catheters serve as a portal of entry for yeast into the urinary system.[3,33] Catheter-associated urinary tract infection represents one of the most common healthcare-associated infections in patients.[36] The presence of a catheter plays a crucial role in the pathogenesis of candiduria; biofilm formation and migration of organisms along the surface of the catheter to organism persistence.[13,17,18,33] *C. albicans* and *C. tropicalis* are the species with the highest adhesion and biofilm formation ability on the urinary catheter. Biofilm is a virulence factor and biofilm affects the development of antifungal resistance.[37] It should be noted that these are the most frequently isolated species in our study.

Study Limitations

The first limitation of this study is that it was performed with a retrospective design. Second, the sample size was small and finally, antifungal susceptibility testing of the isolated yeast species was not performed, thus providing no information on fluconazole resistance trends in isolated fungal strains.

CONCLUSION

In all patients with fungal growth in urine culture, the underlying risk factors should be evaluated first. Depending on the correction of risk factors, fungiuria may resolve spontaneously. This is seen as the best approach both to reduce treatment costs and prevent resistance to antifungals.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Eskişehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (Date: 26.10.2021, Decision No: 10).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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The importance of serum estrone level in cases of chronic venous insufficiency in the lower extremity

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ABSTRACT

Aims: Chronic venous insufficiency (CVI) is a condition characterized by abnormal venous flow dynamics in the lower limbs and is associated with various risk factors such as pregnancy, age, obesity, and high estrogen states. One of these estrogens, estrone, is known to have cardioprotective effects. The study aimed to evaluate the relationship between estrone levels in women with CVI and healthy women.

Methods: Clinical and laboratory data from 39 women with CVI and 31 healthy women without CVI were collected. All participants underwent spectral Doppler examinations and combined B-mode imaging to assess the severity of CVI.

Results: The results showed a statistically significant increase in the diameter of the vena saphenous magna in the CVI group compared to the healthy control group ($p<0.05$). However, there were no significant differences in estrone levels between the two groups. Besides, significant correlations were observed between estrone levels and age (r: -0.351; p=0.028), BMI and age(r: 0.374; p=0.019), and BMI and abdominal circumference (r: 0.700; $p<0.001$) in the CVI group.

Conclusion: Our study suggests that estrone levels may have a protective effect on CVI pathogenesis. The observed effect of estrone on women with CVI may be attributed to its different receptor-level effects compared to estradiol. Further research is necessary to fully elucidate the contribution of estrone to CVI and its underlying mechanisms.

Keywords: Chronic venous insufficiency, estrone, cardioprotective effect, estrogen

INTRODUCTION

Chronic venous insufficiency (CVI) of the lower limbs coincides with a broad clinical range, ranging from asymptomatic but aesthetic abnormalities to severe symptoms.[1] Abnormal venous flow dynamics of the lower limbs are observed in approximately half of the individuals, albeit the estimated prevalence of CVI may vary according to population studies.[2] The risk factors for CVI include prior venous thrombosis, obesity, smoking, family history, pregnancy, advancing age, prolonged standing, a sedentary lifestyle, and high estrogen.[3,4] The presence of varicose veins, skin changes, swelling, leg discomfort, and or ulceration are well-characterized clinical features of CVI. Patients suffering from varicose veins could experience tenderness as a result of venous distension. Varicose veins are characterized by their superficial nature, as well as their bulging and dilated appearance. These veins typically have a diameter of at least 3 mm and exhibit a gradual increase in tortuosity and enlargement over time. A comprehensive physical examination and medical history are essential for establishing a correct diagnosis of CVI. Physical examination should be performed in the upright position to allow maximal distension of the veins. Venous duplex ultrasonography (VDU) is the most prevalent method for diagnosing CVI and provides etiological and anatomical data.[5] VDU provides a combined spectral Doppler and B-mode imaging to detect the presence of venous reflux and insufficiency. The use of color-assisted VDU can help detect venous flow patterns and flow direction. Venous reflux is defined as any noticed reverse flow toward the foot. The Valsalva maneuver, which increases intra-abdominal pressure, can be used to confirm flow characteristics, valve functions, and venous reflux in the central vessels. Venous reflux is revealed by prolonged reverse flow following augmentation.

CVI is known to be associated with high estradiol levels during pregnancy.[6] A study has demonstrated the potential involvement of endogenous estrogens in the development of CVI during the menopausal period.[7]

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The ovaries produce and release two main estrogens, estrone (E1) and estradiol (E2), into circulation. Adipose tissue is also an important source of endogenous estrogens.[8] The peripheral aromatization of testosterone and androstenedione is the main source of circulating E1.[9] Molecular-level studies on estrone have shown potential cardioprotective effects, including vasodilation.[10-12]

In our study, we aimed to evaluate the relationship between estrone levels in women with CVI during the reproductive period and healthy women.

METHODS

Ethical Statement

The study was carried out with the permission of Medicana International İstanbul Hospital Ethics Committee (Date: 03.03.2023, Decision No: 001/2023). All methods were handled in accordance with the regulations and relevant guidelines (principles of the Declaration of Helsinki). Written informed consent was obtained from all of the patients.

Study Design

The clinical and laboratory results of 39 women presenting with CVI in the lower extremity and 31 healthy women without venous insufficiency were evaluated at the Cardiovascular Surgery outpatient clinic of Medicana International İstanbul Hospital through March 2023.

All patients included in the study underwent combined B-mode imaging and spectral Doppler examinations. The diameter of the vena saphena magna at the level of the saphenofemoral junction in the study group was found to be 7.56±0.53 mm, and spectral Doppler ultrasonography revealed stage 3 or 4 insufficiencies in all cases, meeting the criteria for surgical intervention. The control group consisted of asymptomatic individuals. The vena saphena magna diameter at the saphenofemoral junction in the control group was 3.35±0.24 mm, and the spectral Doppler ultrasonographic evaluations indicated no insufficiency (level 0).

Estrone levels were measured between the 2nd and 5th days of menstruation, corresponding to the early follicular phase of the menstrual cycle, in all women included in the study. However, women in the premenarchal and menopausal periods, as well as pregnant women, and those who were using estrogen, progesterone, or gonadotropin-derived hormone replacement for any reason were excluded from the study. All women were required to have passed a minimum of one year since their most recent pregnancy and have regular menstrual cycles. None of the women had any chronic illness that could affect estrone levels or facilitate the formation of varices.

The age range of the women included in the study was 21-47. The demographic data such as age, BMI, waist circumference measurement, gravidity, parity, and smoking status were evaluated.

Blood samples from both patients and controls were collected in the morning between 9-12 am. The blood collection protocol was designed to align with the early follicular phase of the menstrual cycle, between the 2nd and 5th days of menstruation, to eliminate variations in estrone hormone levels due to different cycle days. The serum of these samples was separated through centrifugation at 3500 rpm for 10 min and was stored in eppendorf tubes at -20°C until further analysis. The Estrone levels in the collected serum samples were measured.

Measurement of Estrone levels

BT-LAB, Human Estrone, E1 ELISA KIT (Cat. No. E3035Hu, Bioassay Technology Laboratory, China) was used to determine serum estrone levels. The coefficients of inter- and intra-assay variations were <10% and <8%, respectively. Results are given as pg/ml.

Statistical Analysis

SPSS program (Version 21) (IBM, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to analyze the distribution of all parameters. For normally distributed continuous variables, the results were reported as means standard deviations. The statistical significance of the differences between the means was analyzed by the student's t-test. Pearson's correlation analysis was performed for the correlation analysis. A p-value below 0.05 was accepted to be significant.

RESULTS

The women included in the study were divided into two groups according to the presence of severe CVI in the lower extremities. Age, body mass index, abdominal circumference, gravida, parity, and smoking were recorded as demographic data for both groups (Table 1). There was no age bias between the groups (p>0.05, data not shown).

Table 1. The demographic data of subjects in the control and chronic venous insufficiency groups

The Demography	Controls (n=31)	Chronic venous insufficiency (n=39)	p value
Age (year) (mean±SD)	31.00±7.77	34.44±7.83	0.072
BMI (kg/m²) (mean±SD)	22.90±3.56	24.94±3.87	0.026
Abdominal circumference (cm) (mean±SD)	91.50±9.57	93.73±5.80	0.394
Gravida (mean±SD)	0.71±1.16	1.05±1.19	0.216
Parity (mean±SD)	0.61±1.02	0.90±0.96	0.153
Smoking (n (%))	12 (38.7 %)	7 (17.9 %)	0.052

BMI: Body mass index; VSM: Vena saphena magna; SD: Standard deviation

As the primary results of the study were evaluated, the increase in the diameter of the vena saphenous magna in the CVI group compared to the control group was statistically significant. However, no significant differences were found between the groups in terms of estrone levels (Table 2).

Table 2. Clinical data results of the subjects included in examined groups

Parameters	Controls (n=31)	Chronic venous insufficiency (n=39)	p value
Estrone (ng/L) (Mean±S.D.)	688.19±376.00	528.80±319.82	0.065
VSM diameters (mm) (Mean±S.D.)	3.35±0.24	7.56±0.53	0.001

VSM: Vena Saphena Magna

Besides, a significant correlation between estrone levels and age (r: -0.351; p=0.028), between BMI and age (r: 0.374; p=0.019), and abdominal circumference (r: 0.700; p<0.001) were determined in the CVI group. No significant correlation was found between estrone levels and VSM diameters (Table 3).

Table 3. The Pearson correlation analysis results of the subjects in the chronic venous insufficiency group

		Estrone	BMI	Abdominal circumference	VSM diameters
Age	r	-0.351*	0.374*	0.250	0.087
	p	0.028	0.019	0.124	0.598
Estrone	r	-	-0.138	-0.014	-0.217
	p		0.402	0.933	0.185
BMI	r	-0.138	-	0.700**	0.234
	p	0.402		0.000	0.152
Abdominal circumference	r	-0.014	0.700**	-	-0.137
	p	0.933	0.000		0.406

Statistically significant parameters were shown in bald; r: Pearson correlation coefficient; *: p<0.05; **: p<0.01

DISCUSSION

The presence and high levels of estradiol (increased female population, conditions such as pregnancy) are facilitating factors for the pathogenesis of CVI.[6,7] Despite a few studies suggesting the potential importance of estrogen in the pathogenesis of venous insufficiency, there is a lack of data regarding the significance of estrone levels. The presence of cardioprotective effects, including vasodilation, associated with estrone could explain possible mechanisms in CVI pathogenesis.

Although estrone and its precursor, estradiol, bind to the same receptor, the efficacy of estrone is 10 times lower compared to estradiol.[10-12] Nevertheless, the effects of estrone on both vessels and endothelium suggest that estrone alone may play a role in CVI pathogenesis.

The contribution of estrone to CVI pathogenesis has not yet been fully elucidated. However, based on existing literature, it has been proposed that estrone may contribute to CVI pathogenesis through the potent effect of estradiol and its conversion to estradiol.[13]

In our study, we found that estrone levels in women with CVI were lower compared to the control group, although the difference was not statistically significant. This finding contradicts the expected effect of estradiol.

The higher estrone levels in the control group compared to CVI patients suggest a possible protective effect of estrone in CVI pathogenesis. The observed effect on women with CVI can be explained by the different receptor-level effects of estrone and estradiol on the endothelium. A previous study, supporting our findings, suggested that estrone and estradiol have different effects and physiological impacts at the receptor level.[14]

Various molecular studies have reported increased sensitivity to estrogens at the receptor level in CVI patients.[15-17]

Another distinct finding of our study suggests that estrone, known to be primarily derived from adipose tissue and dramatically increased in postmenopausal periods, may have a protective effect on CVI.

In another study, a direct relationship between estrone and vasodilation and other endothelial functions was reported and low levels of estrone were associated with vascular dysfunction and increased risk of cardiovascular disease.[18] A study investigating the relationship between estrone and vasodilation reported that estrone mediates vasodilation through nitric oxide (NO) via cGMP activation.[19] Studies have shown that NO plays a vasoprotective role through its effects on vasodilation, regulation of leukocyte adhesion, regulation of vascular smooth muscle proliferation, and anticoagulant effects.[20] In another study of CVI, lower plasma NO levels were reported in CVI patients, contributing negatively to CVI pathogenesis.[21] Considering this information, the potential protective effect of estrone on CVI in our study may be explained through its action on NO.

CONCLUSION

However, further molecular-level studies are needed to understand the mechanisms induced by estrone binding to peripheral vascular structures.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medicana International İstanbul Hospital Ethics Committee (Date: 03.03.2023, Decision No: 001/2023).

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Histopathological analysis in functional endoscopic sinus surgery

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ABSTRACT

Aims: The aim of this study is to determine the histopathological diagnosis distribution and benign-malignant ratios of patients who have undergone functional endoscopic sinus surgery (FESS).

Methods: The pathology results of patients who underwent FESS in our clinic between 2018 and 2022 were retrospectively scanned from the hospital database. Demographic characteristics (age, gender) and histopathological findings in the files of the patients were recorded. Histopathological diagnosis distributions and benign-malignant ratios were determined.

Results: A total of 365 patients (262 men (71.8%) and 103 women (28.2%)) were retrospectively scanned from the hospital database. The mean age of the patients was 40.09±13.79 (Mean±SD). The most common histopathological diagnoses were nasal polyp (76.4%), chronic inflammation, edema and congestion (Chronic sinusitis) (16.7%), respectively. Among the malignant tumors, squamous cell carcinoma (0.8%) was observed. Inverted papillomas, which are likely to transform into malignancy, were observed at a rate of 1.0%. Considering the histopathological diagnosis distribution by gender, there was no statistically significant difference ($p>0.05$). Considering the histopathological diagnosis distribution by age, there was a statistically significant difference ($p=0.01$). Malignant pathologies were seen in advanced ages.

Conclusion: The most common histopathological result in patients undergoing FESS is non-neoplastic lesions. However, malignancy diagnoses are encountered, albeit in a small number. Therefore, routine histopathology of FESS is essential to identify pathologies with different prognosis.

Keywords: Paranasal sinuses, endoscopy, pathology, nasal polyps, paranasal sinus neoplasm

INTRODUCTION

Sinonasal diseases are one of the diseases that most frequently require referral to a physician in childhood and adulthood. These diseases mostly respond to medical treatments, but chronic inflammatory, polypoid diseases and mass lesions require surgery.[1]

Functional endoscopic sinus surgery (FESS) has become a safe and effective procedure in the surgical treatment of chronic rhinosinusitis and sinonasal masses, depending on the increase in knowledge of endonasal anatomy and developments in endoscopic and radiological imaging methods. The advantages of FESS over conventional surgical methods are that it is less invasive, causes less damage to the surrounding tissues, leaves no visible scars, and provides a better view of the operation area. Nasal polyps, chronic rhinosinusitis, antrochoanal polyps, mucocele, sinonasal benign and malignant masses are the diseases in which endoscopic sinus surgery is most frequently applied.[2] It has become the most common procedure especially in chronic rhinosinusitis and nasal polyps resistant to medical treatment.[3-5]

Sinonasal neoplasms are a diverse group of tumors originating from the paranasal sinuses and nasal cavity. When sinonasal tumors accompany chronic rhinosinusitis, they may be masked and diagnosis may be delayed. For this reason, all materials removed during surgery are sent for histopathological examination and possible additional diseases are investigated. Paranasal sinus carcinomas are rare and constitute only 3% of all malignancies in the head and neck region.[6] Squamous cell carcinoma (SCC) is the most common tumor, presenting as inverted papillomas or de novo in approximately 10% of cases.[7-9] The paranasal sinuses are air-filled spaces that allow the tumor to grow to substantial size before symptoms and signs develop. Therefore, most patients present at an advanced stage and there is widespread involvement of neighboring regions at the time of diagnosis.[10,11]

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The aim of this study is to evaluate the histopathological results of tissue samples taken during FESS and to determine the histopathological diagnosis distribution and benign-malignant ratios.

METHODS

Ethical Approval

The study was approved by the Kırıkkale University Faculty of Medicine Ethics Committee with the decision numbered 2023.04.09 and dated 19.04.2023. Written informed consent was not obtained because this study was conducted as a retrospective file review. All procedures were carried out in accordance with ethical rules and the principles of the Declaration of Helsinki.

Participants and Study Design

In the study, the files of patients who underwent FESS in the Otorhinolaryngology department of a secondary health care institution between 2018 and 2022 were retrospectively scanned from the hospital automation system. Demographic characteristics (age, gender) and histopathological findings in the files of the patients were recorded. The histopathological diagnosis distribution and benign-malignant ratios of the patients who underwent FESS were determined. Patients whose materials were sent to the pathology department but whose histopathological diagnosis could not be reached in the file archive scan were excluded from the study. All patients who underwent routine and diagnostic FESS were included in the study. Patients who underwent diagnostic FESS were decided by examining the patient files. Patients with certain risk factors in the patient file were recorded as diagnostic FESS. These risk factors are prominent nosebleeds, unilateral pathology, appearance different from chronic rhinosinusitis (CRS) with or without nasal polyps (NP) on nasal endoscopy, palpable cervical lymph nodes, unexplained weight loss, or unexplained structural symptoms (fever, fatigue). Routine FESS procedure was performed in cases of CRS with/without NP and in cases without preoperative clinical suspicion. Unilateral and bilateral FESS cases were recorded. In diagnostic FESS surgery, the material was partially excised. Further treatment options are planned according to the histopathological diagnosis.

FESS Surgery

FESS was performed under general anesthesia with the Messerklinger technique.[2] An infundibulectomy was performed by cutting the anterior attachment of the uncinate process; then the ethmoid bulla was opened and removed. The decision to open the maxillary antrum and explore the posterior ethmoids, frontal recess, and sphenoids was dependent on the extent of the disease, as evidenced by CT scan and surgical findings.

Histopathological Examination

Standard histopathological examination; macroscopic examination, fixation in formalin, decalcification if necessary, sampling of the sample, follow-up stage (with automatic tracking device), blocking of paraffin embedded tissue, section preparation (4-5 microns thick), staining with Hematoxylin-Eosin (HE) and examining the prepared sections under a light microscope.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Normal distribution parameters and Shapiro-Wilk test were used to evaluate the normality of the data distribution. Nominal categorical variables were compared with the chi-square test and Fisher's precision test. Mann-Whitney U and Kruskal-Wallis tests were used for non-parametric variables. Statistical significance level was accepted as $p < 0.05$.

RESULTS

A total of 365 patients 262 men (71.8%) and 103 women (28.2%) who underwent functional endoscopic sinus surgery were retrospectively scanned from the hospital database. The mean age of the patients was 40.09±13.79 (Mean±SD). FESS was applied unilaterally to 34 patients and bilaterally to 331 patients. There were 26 patients who underwent diagnostic FESC in the presence of risk factors. Of 26 patients, 4 were premalignant and 3 were histopathologically malignant. 339 patients had CRS with/without NP or routine FESS without preoperative clinical suspicion. No malignancy was detected in any patient who underwent routine FESS.

When we look at the histopathological diagnoses, the most common nasal polyp was seen with a rate of 76.4%. The second most common diagnosis was chronic inflammation, edema and congestion (chronic sinusitis). It was observed in inverted papilloma and squamous cell carcinoma in the nasal cavity and paranasal sinuses (1.0%, 0.8%, respectively). Histopathological images of the nasal polyp are shown in **Figure 1**, inverted papilloma in **Figure 2**, and squamous cell carcinoma in **Figure 3**.

Considering the histopathological diagnosis distribution by gender, there was no statistically significant difference ($p>0.05$). The histopathological diagnosis distribution by total and gender is given in **Table 1**. Considering the histopathological diagnosis distribution by age, there was a statistically significant difference ($p=0.01$). While the mean age is younger in benign pathologies, malignant pathologies are seen in older ages.

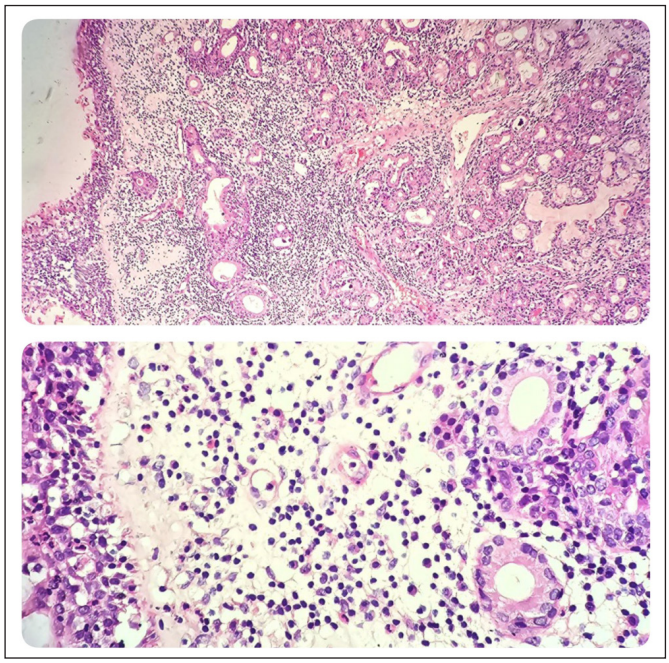

Figure 1. Nasal polyp (upper **Figure** H&E x 100, lower **Figure** H&E x 200)
Top Figure: Inflammatory sinonasal polyp; polypoid sinonasal mucosa with stromal edema, chronic inflammation, and seromucinous gland hyperplasia.
Bottom Figure: Hyalinization of the subepithelial basement membrane and signs of chronic inflammation in the inflammatory sinonasal polyp containing numerous eosinophils.

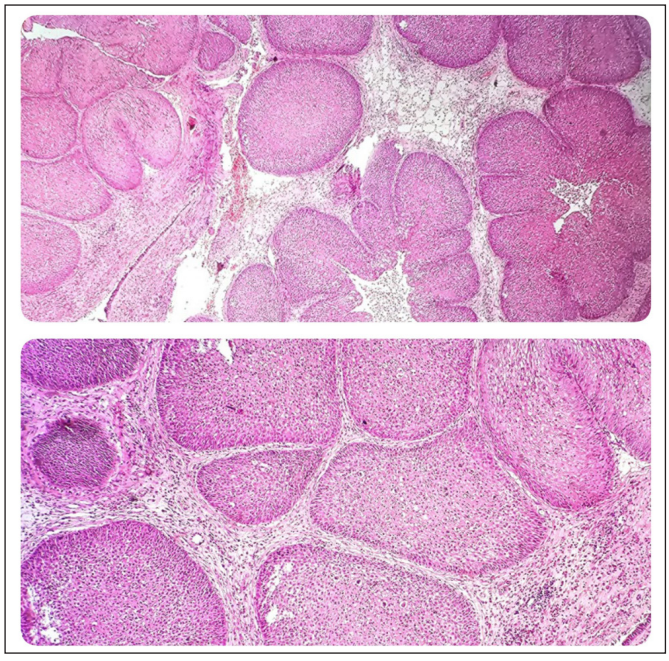

Figure 2. Inverted papilloma (upper **Figure** H&E x 40, lower **Figure** H&E x 100)
In inverted papilloma, the epithelium may be squamous, transitional, or columnar epithelial morphology. Although not clearly visible in our sections, neutrophil migrations and microabscesses into the epithelium can be observed.
Top Figure: The lesion is characterized by thickened-appearing surface epithelium in squamous morphology and inverted pattern with island and cord extensions in the stroma.
Bottom Figure: Although there are no obvious cytological atypia and keratinization findings, chronic inflammation and mild edema may be seen in the stroma.

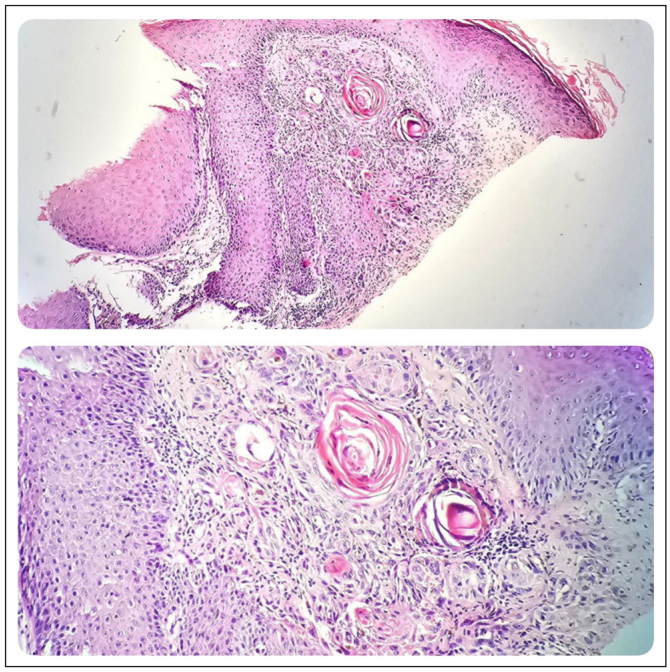

Figure 3. Squamous cell carcinoma (top image H&E x 100, bottom image H&E x 200)
Top Figure: Squamous cell carcinoma; Tumoral lesion with infiltrative pattern originating from squamous epithelium with prominent keratinization, prominent intercellular bridges, mild pleomorphism, mitotic figures in the basal layer and infiltrative islands and small groups under the epithelium.
Bottom Figure: Infiltrative islands formed by squamous cells with extensive eosinophilic cytoplasm with prominent keratin pearl structures in the centre.

Table 1. Histopathological diagnosis distribution in FESS

Pathology	Gender		Total Count (%)
	Male Count (%)	Female Count (%)	
Nasal polyp	207 (74.2%)	72 (25.8%)	279 (76.4%)
Chronic inflammation, edema and congestion (Chronic sinusitis)	37 (60.7%)	24 (39.3%)	61 (16.7%)
Cavernous hemangioma (maxillary sinus)	1 (50.0%)	1 (50.0%)	2 (0.5%)
Pyogenic granuloma	7 (58,3%)	5 (41,7%)	12 (3.2%)
Rhinolite	1 (100.0%)	0 (0.0%)	1 (0.2%)
Benign fibroosseous lesion (mass extending from the anterior maxilla to the floor of the nose)	1 (100.0%)	0 (0.0%)	1 (0.2%)
Inverted papilloma	3 (75.0%)	1 (25.0%)	4 (1.0%)
Squamous cell carcinoma	3 (100.0%)	0 (0.0%)	3 (0.8%)
Dermatofibroma (nasal mucosa)	2 (100.0%)	0 (0.0%)	2 (0.5%)
Total	262 (71.8%)	103 (28.2%)	365 (100.0%)

DISCUSSION

Functional endoscopic sinus surgery is frequently applied in Ear Nose and Throat clinics in our country as well as all over the world. FESS primarily aims to eliminate disease in the paranasal sinuses and to provide sinus ventilation and mucociliary drainage. However, another aim is to facilitate the debridement of diseased tissues and the application of topical treatments to the

mucous membranes of the sinuses.[12] Today, FESS is widely and safely applied in the treatment of bilateral or unilateral benign and malignant sinonasal diseases. The majority of patients are unilateral or bilateral chronic rhinosinusitis and benign sinonasal masses.[13] In our study, benign sinonasal diseases were found in 98.2% of the histopathological examinations. The most common were nasal polyps (76.4%) and chronic sinusitis (16.7%) (CRS). Boer et al.[14] evaluated the postoperative histopathology of 1695 patients who underwent FESS and found that 97.9% of the patients were patients with chronic inflammation with or without polyps. Yaman et al.[15] in their study; In the postoperative histopathological results of 85 patients who underwent bilateral FESS, they found chronic inflammation with or without nasal polyps in all patients. In this study, the most common histopathological lesion after nasal polyps and chronic sinusitis was pyogenic granuloma (3.2%). Pyogenic granuloma is the most common vascular tumor in the nasal cavity. Its etiology is unknown. Two types of hemangiomas have been described in the nasal cavity. The first is pyogenic granuloma and the other is cavernous hemangioma. Pyogenic granuloma constitutes the majority of cases (24). In our study, 2 cavernous hemangiomas (0.5%) and 12 pyogenic granulomas (3.2%) were observed.

Due to the extremely low incidence and rarity of unexpected pathologies of sinonasal tumors, the debate continues regarding the necessity of routine histopathological examination of all nasal specimens. However, some authors suggest that especially malignancy and possible medical legal consequences support routine histological examination.[16] The rate of unexpected diagnosis in bilateral nasal polyp samples ranges from 0% to 0.92%.[17,18] Inverted papilloma is the most common unexpected pathological diagnosis of nasal polyposis.[16,17,19] Inverted papillomas are usually unilateral benign polypoid masses arising from the ectodermal Schneiderian epithelium. Despite its benign histology, it behaves aggressively with local destruction, high recurrence rate and malignant transformation. Although the etiology is not known exactly, a relationship has been found between HPV infection, recurrence rate and malignant transformation.[20] In addition, approximately 11% of inverted papilloma cases are associated with malignancy simultaneously or metachronously.[14] It has been reported that the mean age of inverted papilloma is 55, and the male-female ratio is 2-5/1.[21] In this study, inverted papilloma was seen in 4 (1.0%) patients, with a mean age of 49.5 years and a male-female ratio of 3/1. Garavello and Gaini examined 2147 patients and found inverted papilloma in seven and adenocarcinoma in one.[16] Diamantopoulos et al.[17] In their study in which they examined 2,021 patients, they found 11 inverted papillomas, 1 adenocarcinoma, and 3 squamous cell carcinomas. In the study of Romashko and Stankiewicz on 277 patients with nasal polyps, no unsuspected pathology was found.[18] Kale et al.[19] only one case of inverted papilloma was found. In the meta-analysis of 3772 patients, only 3 unexpected malignant diagnoses and 18 unexpected benign diagnoses were found.[13]

In our study, in which we evaluated the histopathological results of 365 patients retrospectively, we observed SCC in only 3 (0.8%) patients and inverted papilloma in 4 (1.0%) patients. There was no unexpected diagnosis. They were clinically suspicious cases and diagnostic FESS was performed. All of the malignant and premalignant lesions were patients who underwent unilateral FESS. Patients with neoplastic specimens were significantly older than those with benign specimens. Age correlated with neoplasm, while gender did not differ between patients with neoplasms and patients with inflammatory lesions. Sinonasal tumors have the highest incidence in the fifth to seventh decades and are predominantly male. All 3 SCC cases in our study were male and the mean age was 60.3.

Finally, we acknowledge that the retrospective nature of the study may be an important shortcoming and large-scale prospective studies are needed.

CONCLUSION

FESS surgery is recommended because of easy access to intranasal masses, easy and complete removal of the pathological lesion, short operation time and minimally invasiveness. Benign pathologies constitute the majority of paranasal sinus samples taken after FESS surgery. It is rarely seen in malignant pathologies. It was concluded that early diagnosis of premalignant and malignant pathologies could be possible with routine histopathological sampling.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 19.04.2023, Decision No: 2023.04.09).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Original Article

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Evaluation of the association of anti-thyroid peroxidase with antinuclear antibodies and different antinuclear antibodies patterns

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ABSTRACT

Aims: To investigate the relationship between anti-thyroid peroxidase (TPO), a marker for Hashimoto's thyroiditis, and antinuclear antibodies (ANA) and ANA patterns, biomarkers for systemic autoimmune diseases.

Methods: In this study, ANA and anti-TPO test results, obtained in our hospital laboratory between 2019 and 2022, were retrospectively evaluated. ANA was detected by the indirect immunofluorescence antibody method using commercial HEp-20-10 cell substrates and anti-TPO was determined by the sandwich immunoassay method using a commercial immunoassay analyzer.

Results: A total of 1750 patients' results were analyzed. ANA was positive in 28.7% of anti-TPO-positive patients and 19% of anti-TPO-negative patients. While 6.4% (112/1750) of patients were positive for both ANA and anti-TPO, both test results were negative in 62.85% of patients ($p<0.001$). When the ANA patterns' distribution in patients with ANA and anti-TPO positivity examined together, the homogeneous pattern was statistically significantly higher than the other patterns ($p=0.043$).

Conclusion: Individuals with autoimmune thyroid disease had a higher rate of autoantibodies not only to thyroid-specific antigens but also to non-thyroid-specific antigens. Further studies are needed on how epigenetic changes, such as histone modifications might cause other autoimmune diseases and increase their frequency.

Keywords: Autoimmunity, antinuclear antibodies, autoimmune disease, thyroid diseases, Hashimoto disease

INTRODUCTION

Autoimmune diseases affect the quality of life and increase health care costs. When there are multiple causes of death due to autoimmune diseases, mortality increases at least 1.5-fold.[1] Autoimmune diseases, estimated to have a prevalence of about 5% in developed countries, are more common in women.[2]

The main factors involved in the development of autoimmunity are infections, other environmental factors, and genetic predisposition. When autoreactive B and T cells are stimulated under the influence of these factors, autoimmune diseases develop due to formation of antibodies or cellular immune responses against autoantigens.[3]

Autoimmune diseases can be systemic or organ specific. The most commonly used parameter in screening for systemic autoimmune diseases is the detection of antinuclear antibodies (ANA).[4,5] In organ-specific autoimmune diseases, antibodies that directly target antigens in an organ or endocrine gland cause tissue damage, and the goal is to detect these antibodies in screening.[6] The best example of this group is anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) antibodies, which cause tissue damage in Hashimoto's thyroiditis.[7]

Because of the changes that can occur in autoimmune pathogenesis, other autoimmune disorders accompany the original disease in 25% of patients.[8] The incidence of multiple autoimmune diseases has been reported to be 33-45% for Systemic Lupus Erythematosus (SLE), 13-32% for Rheumatoid Arthritis, 26% for Systemic Sclerosis, 33-52% for Sjögren's syndrome, and the most common accompanying disease is autoimmune thyroid disease.[9] The overlap between Hashimoto's thyroiditis and some non-specific rheumatic symptoms has been reported to predict the development of some connective tissue diseases.[10]

Therefore, in this study, the association between anti-TPO, one of the markers for Hashimoto's thyroiditis, and ANA, a marker for systemic autoimmune disease, and different ANA patterns was investigated to reveal the presence of organ-specific autoimmune thyroid disease along with systemic autoimmune disease.

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METHODS

The study was carried out with the permission of University of Health Sciences İzmir Tepecik Training and Research Hospital Non-interventional Ethics Committee (Date: 15.04.2022, Decision No: 2022/04-23). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

ANA and anti-TPO test results of samples sent to the Medical-Microbiology and Medical-Biochemistry Laboratory of İzmir Tepecik Training and Research Hospital between 2019 and 2022 were retrospectively evaluated. The patients' data were obtained from the hospital medical records. Patients with both anti-TPO and ANA test results were included in the study. The first samples of patients were accepted. Other samples were excluded.

Indirect Immunofluorescence Antibody (IIF)- ANA Scanning

ANA was detected by the IIF method using commercial HEp-20-10 cell substrates (Euroimmun Luebeck, Germany). Testing and scoring were performed according to the manufacturer's instructions with an initial screening dilution of 1:100. After slide preparation, the test was scored according to the international consensus report on ANA samples.[11]

Anti-TPO Detection

Anti-TPO was determined by the sandwich immunoassay method using a commercial immunoassay analyzer (DxI 800, Beckman Coulter, Inc., CA, USA). The analytical range of the assay reported by the manufacturer is 0.25-1000 IU/mL, the analytical sensitivity is 0.25 IU/mL, and the reference range reported for the healthy adult population is 0-10 IU/mL.

Statistical Analysis

The SPSS (Statistical Packages for the Social Sciences) version 22.0 program (SPSS Inc., Chicago, USA) was used for the statistical analysis. The qualitative results of the tests (positive/negative) and the sex of the patients were recorded as categorical variables, and the age of the patients was recorded as a continuous variable. Numerical data were expressed as mean±standard deviation (SD), number (n), and percentage (%). The chi-square test was used to compare categorical variables such as anti-TPO positivity, ANA positivity, and sex. Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to analyze the normality assumption for groups such as sex and ANA patterns of continuous variables such as age. Analysis continued with parametric tests in the case of a normal distribution and nonparametric tests in the case of an abnormal distribution. Comparison of categorical variables by patient age was performed with Independent Sample T, One-Way Anova, and Mann-Whitney U tests. The Spearman correlation test was used to analyze the correlation between test dilutions of ANA, and anti-TPO levels. Post hoc tests were used for further pairwise comparisons. The statistical significance level (p value) was set at 0.05 for all analyzes.

RESULTS

In the study, 1750 patients (mean age±SD=40.0± 19.0) (76.5% female, 23.5% male) routinely screened for ANA, and anti-TPO tests from different clinics were included.

ANA and anti-TPO positivity were found in 21.2% (371/1750) and 22.3% (391/1750) of patients respectively. ANA was positive in 28.7% of anti-TPO-positive patients and 19% of anti-TPO-negative patients (p>0.001). Both ANA and anti-TPO positivity were detected in 6.4% of patients (112/1750), while both were negative in 62.85% (1100/1750) of patients. Anti-TPO positivity in patients with ANA positive test results and anti-TPO negativity in patients with ANA negative test results were statistically significant (p<0.001) (Table 1).

Table 1. Comparison of ANA and anti-TPO test results

	Anti-TPO positive	Anti-TPO negative	Total	p
ANA positive (n=371)	112	259	371	<0.001
ANA negative (n=1379)	279	1100	1379	
Total	391	1359	1750	

The most common IIF-ANA pattern detected in both ANA positive and anti-TPO positive patients (n:112) was homogeneous (n:43, 38.4%), followed by dense fine speckled (DFS)-70 (n:29, 25.9%), granular (n:26, 23.2%), nucleolar (n:6, 5.4%), nuclear membrane (n:5, 4.5%), nuclear dots (n:2, 1.8%), and centromere (n:1, 0.8%) (p=0.057, chi-squared) (Table 2).

Table 2. Relationship between positive ANA patterns and anti-TPO results (n=371)

	Anti-TPO positive, n=112	Anti-TPO negative, n=259	p*
Homogeneous (n=114)	43 (38%)	71 (27%)	0.035
DFS-70 (n=78)	29 (26%)	49 (19%)	0.130
Centromere (n=13)	1 (1%)	12(5%)	0.120
Speckled (n=110)	26 (23%)	84 (32%)	0.074
Nucleolar (n=29)	6 (5%)	23 (9%)	0.246
Nuclear envelope (n=16)	5 (5%)	11 (4%)	1.000
Nuclear dots (n=11)	2 (2%)	9(4%)	0.516

*Each group was tested against other patterns (chi-square)

When the ANA patterns' distribution in patients with ANA and anti-TPO positivity were examined together, the homogeneous pattern was found to be significantly higher than the other patterns (p=0.035, chi-square)

(Table 2). When the results were evaluated according to staining in the metaphase layer, a central element in the evaluation of ANA, ANA metaphase positivity was found to be statistically higher (n:73) in patients with anti-TPO positivity (p=0.001, chi-square) (Table 2). There was no statistically significant difference for DFS-70 (p=0.13), centromere (p=0.12), speckled (p=0.074), nucleolar (p=0.246), nuclear envelope (p=1), nuclear dots(p=0.516). No correlation was found between test dilutions of ANA, and anti-TPO levels (r=-0.01, p=0.80). There was no statistically significant difference between the age of patients who were simultaneously positive for ANA and TPO (p=0.361, Oneway Anova). The age and sex distribution of ANA positive patients showed in Table 3.

Table 3. The age and sex distribution of ANA positive patients (n=371)

	Age,mean±SD years	Women, n (%)
DFS-70 (n=78)	36.09± 17.59	64 (82%)
Homogeneous (n=114)	44.45±20.14	95 (83%)
Speckled (n=110)	36.83±19.63	83 (76%)
Nucleolar (n=29)	42.20±21.48	22 (76%)
Nuclear dots (n=11)	41.12±19.15	9 (82%)
Nuclear envelope (n=16)	54.73±16.47	14 (88%)
Centromere (n=13)	43.87±19.90	10 (77%)

DFS70: dense fine speckled 70; SD: standard deviation.

DISCUSSION

The most important elements in the development of autoimmune diseases (AD) are genetic predisposition and environmental factors.[12] Autoimmune diseases may develop as a result of disturbances in the regulation of the immune system due to these factors. Polyautoimmunity is defined as the presence of more than one autoimmune disease in a single patient, and in 13-52% of patients, other autoimmune diseases occur in addition to the original disease, with the most common concomitant disease being autoimmune thyroid disease.[9]

ANA positivity with low titers can also be observed in healthy individuals and in many different non-rheumatic diseases. An abnormal ANA should be a titer that is above the 95th percentile of a healthy control population.[13] In the current study, the ANA prevalence was 28.7% in anti-TPO positive patients with our ANA screening dilution (p <0.001). Prevalence studies of systemic autoantibodies in individuals with thyroid disease are limited. The prevalence of ANA in autoimmune thyroid disease patients was reported to be 35% by Tektonido et al.[14], 45% by Lazurova et al.[15], and 26% by Morita et al.[16]

In a study evaluating patterns with ANA in anti-TPO-positive individuals, a prevalence of 18% was found. The ANA patterns were found to be homogeneous in 50% and granular in 35% of anti-TPO-positive patients, but the DFS-70 pattern was not examined.[8] In the current study one of the nuclear patterns, DFS-70 was evaluated for the first time and our results suggest that DFS-70 and homogeneous patterns were significantly higher in anti-TPO positive patients.

The homogeneous pattern was the most frequent in the anti-TPO-positive patients. The antigens associated with the homogeneous pattern were dsDNA, histone, and nucleosome. In a study evaluating the extractable nuclear antigen (ENA) profile,[8] the prevalence of homogeneous patterns in anti-TPO positive patients was 50%, like our study (when the DFS-70 pattern was excluded, the prevalence of homogeneous pattern was 52%), and the prevalence of antibodies to histones was very high at 72%. The homogeneous pattern is more common in patients with SLE but can also be found in patients with mixed connective tissue disease and drug-induced lupus.[17] Therefore, follow-up and evaluation of patients with homogeneous patterns in ANA screening and histone positivity in ENA evaluation concerning anti-TPO may be useful for the early diagnosis of Hashimoto's thyroiditis. The overlap between Hashimoto's thyroiditis and some non-specific rheumatic symptoms has been reported to predict the development of some connective tissue diseases.[10]

In this study, the DFS-70 pattern, which has a high prevalence in the healthy population and correlates negatively with ANA-related autoimmune diseases, was the second most common (26%) pattern in anti-TPO-positive patients. In a study investigating the relationship between DFS-70 autoantibodies and other autoantibodies, the most common concomitant autoantibody was anti-TPO at 16%.[18] This rate was higher in this study and anti-TPO was positive in 37% (29/78) of DFS-70-positive patients. Therefore, it may be important to perform the anti-TPO test when the DFS-70 pattern is detected in healthy individuals, allergic diseases, non-systemic autoimmune diseases, ocular diseases, or cancers. Future studies are needed in these disease groups. No association between thyroid diseases and patterns other than homogeneous and DFS-70 has been described.

One of the limitations of our study is that it was a retrospective study, meaning that we could not determine which antibody appeared first and influenced the other or whether these autoantibodies were persistent or transient. We also do not know how these antibodies change with treatment. Second, we were unable to reveal whether cross-reactivity of the substrates used to detect these antibodies led to false positive results.

CONCLUSION

Individuals with autoimmune thyroid disease have a high rate of autoantibodies not only to thyroid-specific antigens but also nonspecific ones. Although there are many studies on epigenetics, the epigenetic changes in thyroid autoimmune diseases have not fully elucidated.[19-22] There is a need for further prospective studies on how epigenetic alterations, such as histone modifications may cause systemic autoimmune diseases and increase their frequency in autoimmune thyroid diseases. Those will provide new information that can adopted in the diagnosis, follow-up, and prognosis of thyroid disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Tepecik Training and Research Hospital, Non-interventional Clinical Researches Ethics Committee (Date: 15.04.2022, Decision No: 2022/04-23).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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Treatment selection for T4 laryngeal cancer: is organ-preserving approach possible with chemoradiotherapy or is multimodality treatment more effective?

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ABSTRACT

Aims: Organ-preserving approach is recommended as an evidence-based treatment option for advanced laryngeal cancer (LC) with similar survival results. However, the organ-preserving approach in T4 disease is controversial, and surgical treatment is primarily preferred. Today, chemoradiotherapy (CRT) is applied to T4 LC patients who are inoperable for medical or surgical reasons and upon the request of the patient who refuses the recommended surgical treatment. The aim of this study was to evaluate the treatment outcomes in patients with T4 LC who underwent CRT for these conditions and received adjuvant radiotherapy (RT)/CRT as the standard treatment regimen after surgery.

Methods: A retrospective review of T4 LC patients treated with CRT (17 patients) and adjuvant RT/CRT (26 patients) between 2015 and 2021 was conducted. Overall survival (OS), local regional recurrence-free survival (LRRFS), and disease-free survival (DFS) were compared between the groups. The organ preservation rate was determined for the CRT group.

Results: The median follow-up time for the entire cohort was 41 months, the 5-y OS, LRRFS, and DFS were 55.9%, 51.4%, and 51.9%, respectively. Statistically significant difference was found between the treatment groups in terms of 5-y OS, LRRFS, and DFS rates, and survival was found to be decreased in the CRT group (35.3% vs. 70.2%, p=0.007; 22.1% vs. 75.1%, p= 0.001; 22.1% vs. 75.7%, p=0.001). With respect to other clinicopathological factors, age was the only significant factor in on OS in multivariate analysis, whereas tumor size, nodal stage, and ECE (in the postoperative RT group, except LRRFS) were linked with OS, LRRFS, and DFS rates. Among the patients who underwent CRT, OS was found to be better in the group applied due to the patient's request compared to the patients referred for RT due to medical or surgical inoperability, and in multivariate analysis, the indication for RT remained an independent predictor of OS. In addition, the 3-y organ preservation rate was 81.5% in the CRT group.

Conclusion: The surgical arm had statistically significantly superior results in terms of OS, LRRFS, DFS compared to the CRT group. However, it is also noteworthy that OS was better in cases where RT is applied at the patient's request without inoperable disease. In addition, laryngeal protection was observed to a large extent in the CRT arm.

Keywords: Laryngeal cancer, advanced stage, organ preservation, radiotherapy, laryngectomy, treatment outcome

INTRODUCTION

Among head and neck squamous cell carcinomas, laryngeal malignancies are the most prevalent.[1] Treatment modalities for early-stage laryngeal cancer (LC) are either primary radiotherapy (RT) or endoscopic resection, both of which aim to preserve laryngeal function and share similar survival and functional outcomes, but the optimal primary treatment modality for advanced LC is controversial.[2] In the Veterans Affairs larynx study in 1991, an organ-preserving approach, provided by RT after induction chemotherapy (CT), was proposed as a valid alternative to total laryngectomy (TL) for locally advanced LC.[3] Subsequently, the Radiation Therapy Oncology Group (RTOG) 91-11 study, the results of which were announced in 2003, examined the timing of RT and the use of concomitant CT. It was shown that concomitant chemoradiotherapy (CRT) provides higher laryngeal protection rates than either RT following induction CT or RT alone.[4] Following these landmark prospective randomized studies, organ-preserving approaches have been adopted in advanced LC, and CRT has become the treatment of choice.

Although oncological results are very successful in T2, T3, and node-positive disease, this situation is controversial in T4 disease. The majority of patients

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enrolled in the RTOG 91-11 study were at stages T2 and T3. T4 tumors comprised approximately 10%, but only low-volume T4 tumors were included. Moreover, the Veterans Affairs study also showed a higher rate of local recurrence in the non-surgical arm of T4 disease. The results obtained from these studies have led clinicians to interpret that surgical treatment should be preferred instead of an organ-preserving approach in T4 disease.

However, TL causes deterioration of swallowing and speech functions and also decreases the quality of life due to the psychosocial problems it will bring, so patients may refuse surgical treatment and desire for CRT.[6] CRT is also indicated in patients who are surgically inoperable, as is the case with disease extending beyond the larynx. Apart from this, CRT may be the only alternative for patients who are in the high-risk group in terms of operation due to comorbid diseases. In addition, an organ-preserving approach may be preferred according to the decision of the multidisciplinary committee, as in the RTOG 91-11 study, in low-volume T4 tumors.

The purpose of this study was to retrospectively screen the patients with a clinical diagnosis of T4 LC who underwent CRT for these conditions and patients with a pathological diagnosis of T4 LC who underwent postoperative RT/CRT (multimodality treatment), to compare survival rates between groups, and identify the variables that may have an impact on the oncological outcome.

METHODS

The study was carried out with the permission of Samsun University Clinical Researches Ethics Committee (Date: 12.04.2023, Decision No: 2023/7/17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.[7]

Study Population

Between January 2015 and December 2021 in Samsun Training and Research Hospital, patients who were diagnosed with T4 LC clinically and treated with CRT with an organ-preserving strategy and patients with a pathological diagnosis of T4 LC who underwent postoperative RT/CRT were identified retrospectively. Patients who received palliative RT and had metastatic disease at the time of the initial diagnosis were not included in the study.

The patient's clinical data, including demographic information and treatment outcomes, was collected from the patient's medical records. The following data were recorded for each patient: age, gender, date of diagnosis, tumor location, tumor extent, tumor size, tumor volume, vocal cord fixation, thyroid-cricoid cartilage involvement, lymph node involvement, presence of surgery, lymphovascular invasion, perineural invasion, extracapsular extension (ECE), dose and fraction number of applied RT, concurrent CT information, total or partial laryngectomy, and type of lymph node dissection.

Treatment

A multidisciplinary head and neck tumor board decided whether to have surgery, taking into account the medical condition of each patient and the characteristics of the disease. In addition, the patient's request was also effective in the treatment decision. Most patients underwent surgical treatment consisting of TL with bilateral neck dissection, TL with bilateral neck dissection and hemithyroidectomy, or partial laryngectomy with bilateral neck dissection.

RT was delivered using with the intensity-modulated RT technique. Dose fractionation schedules for RT were implemented as follows: In definitive RT, a total of 70 Gy was given to the primary tumor and involved node(s), 60 Gy to the larynx and the high-risk lymph node groups, and 50-54 Gy to the low-risk lymph node groups with a daily fraction of 2 Gy. In some patients, the simultaneous integrated boost technique was used with a total dose of 69.96 Gy, 59.4 Gy, and 54.12 Gy in 33 fractions. In postoperative RT, a total of 60 Gy was delivered to the tumor bed and the high-risk lymph node groups, and 50-54 Gy to the low-risk lymph node groups with a daily fraction of 2 Gy. Patients with positive surgical margins or lymph nodes with ECE were given 66 Gy.

Concurrent CT was applied to patients who underwent definitive RT. In the presence of risk factors, CT was administered concurrently with adjuvant RT. Low-dose cisplatin (35-40 mg/m^2 weekly during RT) or high-dose cisplatin (75-100 mg/m^2 days 1, 22, and 43) were preferred regimens. Carboplatin or cetuximab are alternative concomitant systemic agents for patients deemed medically unfit to tolerate cisplatin.

Follow-up

The first clinical examination was performed 1 month after the completion of RT, and the response assessment was performed at 2 months. Further follow-up examinations were performed every 3 months for the first 2 years, every 6 months for the next 3 years, and once a year thereafter. Laryngoscopic and physical examinations were used to monitor patients. Head and neck MRI or CT scans and PET/CT were performed 2-3 months after the end of RT to assess response to

treatment and then when clinically necessary. Tumor re-development in the primary region was defined as local recurrence, and the detection of lymph nodes was defined as regional recurrence. Any metastasis found in solid organs was considered a distant metastasis. Salvage surgery was performed in patients with local regional recurrence and in the presence of residual disease after CRT. In the presence of distant metastases, CT and/or RT were applied.

Endpoints

The primary endpoints analyzed were overall survival (OS), local regional recurrence free survival (LRRFS), and disease-free survival (DFS). OS was defined as the period of time from the time the patients were diagnosed with LC until the last follow-up or death. LRRFS was defined as the period of time from the time the patients were diagnosed with LC until the locoregional recurrence or death, whichever occurred earlier. DFS was defined as the period of time from the time the patients were diagnosed with LC until the locoregional recurrence, distant recurrence, or death, whichever occurred earlier. The secondary endpoint analyzed was the organ preservation rate. Organ preservation rate was defined as the the period of time between the date of diagnosis and the date of salvage surgery. The last follow-up date and survival status were updated in May 2023.

Statistical Analysis

Statistical analyses were performed using SPSS statistical software (version V25.0; IBM Corporation, Armonk, NY, USA). Continuous variables are presented as medians after examining with normality tests, and categorical variables are presented as the frequency and proportion (%). Chi-square test or Fisher exact test were used to compare variables between the groups. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression was used to determine hazard ratios (HR). A p-value less than 0.05 was considered statistically significant.

RESULTS

Patients, tumor, and treatment characteristics were summarized in Table 1. A total of 43 eligible patients were identified, including 17 treated with definitive CRT and 26 receiving RT/CRT following surgery. There was no statistically significant difference between the treatment groups in terms of patient and tumor characteristics (Table 2). CRT was preferred in 8 of 17 patients due to the patient's request, and in 9 of them because they were surgically inoperable or in the high-risk group due to comorbid diseases.

Table 1. Baseline clinicopathological characteristics of the patients with laryngeal carcinoma

Variable	Patients (43) n (%)
Age (median)	59 (49-81)
Gender	
Female	2 (4.7)
Male	41 (95.3)
Smoking	
Yes	28 (65.1)
No	2 (4.6)
Not reported	13 (30.3)
Localization	
Glottic/Transglottic	21 (48.8)
Supraglottic	22 (51.2)
Comorbidity	
Diabetes	4 (9.3)
Hypertension	17 (39.6)
Heart disease	13 (30.3)
Lung disease	11 (25.6)
No	15 (34.9)
Anterior commissura invasion	
Yes	26 (60.5)
No	17 (39.5)
Subglottic extension	
Yes	25 (58.1)
No	18 (41.9)
Cartilage involvement	
Yes	40 (93)
No	3 (7)
T stage	
T4a	28 (65.1)
T4b	15 (34.9)
N stage	
N0-1	31 (72.1)
N2-3	12 (27.9)
Surgery	
Yes	26 (60.5)
No	17 (39.5)
Surgery Type	
TL	25 (96.2)
PL	1 (3.8)
Dissection	
BBD	13 (50)
BBD+HT	13 (50)
Lymphovascular invasion	
Yes	13 (50)
No	13 (50)
Perineural invasion	
Yes	7 (26.9)
No	19 (73.1)
Extracapsular extension	
Yes	2 (7.7)
No	24 (92.3)
Surgical margin	
Yes	1 (3.8)
No	16 (61.6)
Close	9 (34.6)
Treatment	
Definitive CRT	17 (39.5)
Adjuvant RT	4 (9.3)
Adjuvant CRT	22 (51.2)
RT Schedule/Dose	
Definitive	8 (50)
70 Gy, conventional	8 (50)
69.96 Gy, SIB	5 (19.1)
Adjuvant, conventional	2 (7.7)
66 Gy	19 (73.2)
64 Gy	
60 Gy	
Chemotherapy schema	
Once a week (35-40 mg/m²)	33 (87.2)
Once every 21 days (75-100 mg/m²)	5 (12.8)

BBD: Bilateral Neck Dissection; CRT: Chemoradiotherapy; HT: Hemithyroidectomy; PL: Partial Laryngectomy; RT: Radiotherapy; SIB: Simultaneous Integrated Boost; TL: Total Laryngectomy

Table 2. Baseline clinicopathological characteristics of the patients with definitve CRT and adjuvant RT/CRT

Variable	Adjuvant RT/CRT Patients, 26 (n,%)	Definitive CRT Patients, 17 (n,%)	p
Age			
<60	19 (67.9)	9 (32.1)	0.176
≥60	7 (46.7)	8 (53.3)	
Performance status			
ECOG 0-1	21 (67.7)	10 (32.3)	0.097
ECOG 2	5 (41.7)	7 (58.3)	
Gender			
Female	2 (100)	0 (0)	0.511
Male	24 (58.5)	17 (41.5)	
Anterior commissura invasion			
Yes	17 (65.4)	9 (34.6)	0.415
No	9 (52.9)	8 (47.1)	
Subglottic extension			
Yes	17 (68)	8 (32)	0.234
No	9 (50)	9 (50)	
Tumor size			
<3.5 cm	8 (50)	8 (50)	0.280
≥3.5 cm	18 (66.7)	9 (33.3)	
T stage			
T4a	17 (60.1)	14 (45.2)	0.964
T4b	9 (60)	3 (25)	
N stage			
N0-1	17 (54.8)	14 (45.2)	0.306
N2-3	9 (75)	3 (25)	
Cartilage involvement			
Yes	24 (60)	16 (40)	0.658
No	2 (66.7)	1 (33.3)	

CRT: Chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; RT: Radiotherapy

The median follow-up time for the entire cohort was 41 months, with a range from 7 months to 97 months. Seventeen died at the end of the follow-up period. For the entire cohort, the 5-y OS was 55.9%, and the mean OS was 64.87 (HR=6.04, 95% confidence interval (CI): 53.05-76.69 months, and the median OS was not reached. A statistically significant difference was found between the treatment groups in terms of 5-y OS rates, with 70.2% in the adjuvant RT/CRT arm and 35.3% in the CRT arm (**Figure 1a**, p=0.007). With respect to other clinicopathological factors, patients <60 years old (p=0.037), tumor size <3.5 cm (p=0.035), tumor volume <20 cc (p=0.028), nodal stage 0-1 (p=0.013), and the absence of ECE (p=0.009) were associated with improved OS (**Table 3**). Among the patients who underwent definitive RT, OS was found to be better in the group applied due to patient demand compared to the patients referred for RT due to medical or surgical inoperability (**Figure 2a**, p=0.012). Primary treatment modality, age, tumor size, nodal stage, the indication of RT, and ECE (in the postoperative RT group) were independent predictors of OS on multivariable analysis (**Table 4**).

Table 3. Univariate analysis for factors influencing OS, LRRFS and DFS in patients with laryngeal cancer

Variable	OS			LRRFS			DFS		
	3-y	5-y	p	3-y	5-y	p	3-y	5-y	p
Age									
<60	73.3	66.7	0.037	66	58.7	0.107	67.2	59.8	0.139
≥60	53.3	38.1		40	0		40	40	
Localisation									
Supraglottic	56.5	33.5	0.124	47	47	0.498	47.7	47.7	0.302
Glottic/Transglottic	75.9	70.5		66	58.7		66.3	59	
Tumor Size (cm)									
<3.5	87.1	79.1	0.035	85.7	71.4	0.034	85.7	71.4	0.033
≥3.5	49.5	41.3		42.3	42.3		43	43	
Tumor Volume (cc)									
<20	71.6	62.5	0.028	63	56.7	0.076	63.4	57.1	0.119
≥20	17.9	0		19	0		19	0	
Cartilage involvement									
Yes	69.1	63	0.097	61	55.5	0.007	61.3	55.89	0.009
No	33.3	0		0	0		0	0	
T stage									
T4a	66.8	62	0.597	62.9	55.9	0.282	63.2	56.1	0.354
T4b	58.2	43.6		45	45		45.7	45.7	
N stage									
N0-1	76.6	68.8	0.013	66.6	59.2	0.018	66.4	59.4	0.013
N2-3	38.9	25.9		30	30		31.3	31.3	
Treatment									
Adjuvant RT/CRT	791	70.2	0.007	75.1	75.1	0.001	75.7	75.7	0.001
Definitive CRT	41.2	35.3		29.4	22.1		29.4	22.1	
RT indication									
Patient request	66.7	66.7	0.012	33.3	33.3	0.073	33.3	33.3	0.073
Inoperable	11.1	0		11.1	0		11.1	0	
Extracapsular extension									
Yes	0	0	0.009	0	0	0.039	0	0	0.014
No	86.7	77		82.5	82.5		82.6	82.6	

CRT: Chemoradiotherapy; DFS: Disease-Free Survival; LRRFS: Local Regional Recurrence Free Survival; OS: Overall Survival; RT: Radiotherapy

Table 4. Multivariate analysis for factors influencing OS, LRRFS and DFS in patients with laryngeal cancer

Variable	OS		LRRFS		DFS	
	HR	p	HR	p	HR	p
Age <60 vs ≥60	3.55(1.17-10.74)	0.029	-	-	-	-
Tumor Size (cm) <3.5 vs ≥3.5	3.78(1.14-12.50)	0.024	3.46(1.00-11.95)	0.049	3.49(1.01-12.04)	0.048
N stage N0-1 vs N2-3	10.43(2.80-38.76)	< 0.001	2.86(1.14-7.18)	0.025	2.99(1.19-7.49)	0.019
Treatment Adj RT/CRT vs Def CRT	7.69(2.07-23.67)	<0.001	9.35(2.28-27.63)	<0.003	8.53(2.12-24.98)	<0.002
RT indication Patient request vs Inoperable	0.16(0.03-0.81)	0.027	-	-	-	-
Extracapsular extension Yes vs No	0.07(0.009-0.67)	0.020	0.20(0.03-1.11)	0.066	0.15(0.02-0.85)	0.032
Cartilage involvement Yes vs No	-	-	4.85(1.35-17.45)	0.015	4.49(1.24-16.23)	0.022

CRT: Chemoradiotherapy; DFS: Disease-Free Survival; HR: Hazard Ratio; LRRFS: Local Regional Recurrence Free Survival; OS: Overall Survival; RT: Radiotherapy

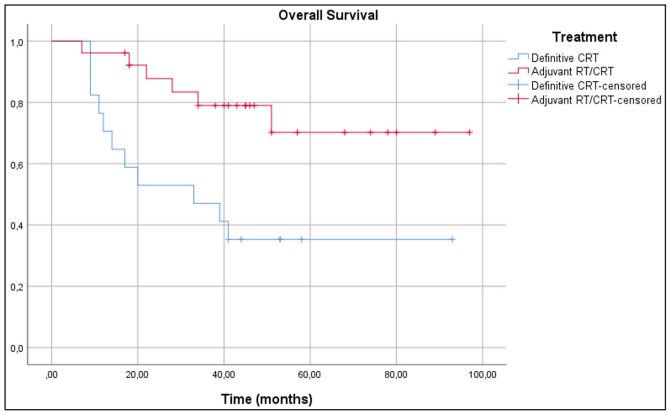

Figure 1a. Kaplan-Meier graph of OS comparing definitive CRT versus adjuvant RT/CRT.

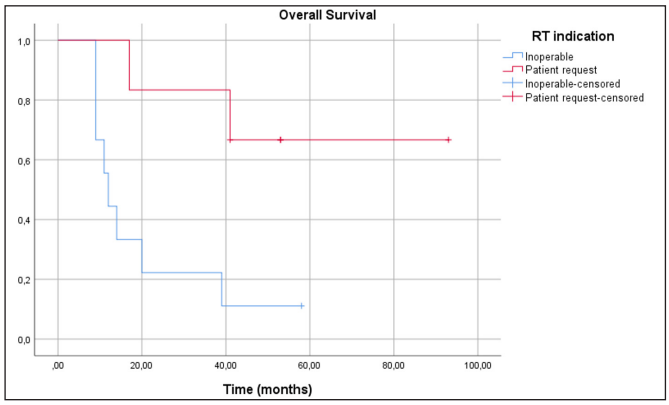

Figure 2a. Kaplan-Meier graph of OS evaluating definitive CRT according to RT indication.

At a median time of 13 months (range: 7-52) after RT, 9 individuals experienced recurrence. Most recurrences were in the definitive CRT group, with 7 patients, of whom 2 patients without distant metastases underwent salvage surgery. Lymph node excision was performed in one patient who developed regional recurrence in the adjuvant treatment group. Distant metastases were detected previously or simultaneously in four of the patients who relapsed, and CT was initiated in these patients. A recurrence in one patient was detected during the last follow-up, and a treatment plan has not been made yet. The best supportive care was applied to one patient because of poor performance.

For the entire cohort, the 5-y LRRFS was 51.4% and the mean LRRFS was 60.22 (HR=6.27, 95% CI: 47.92-75.51) months, and the median LRRFS was not reached. A statistically significant difference was found between the treatment groups in terms of 5-y LRRFS rates, with 75.1% in the adjuvant RT/CRT arm and 22.1% in the CRT arm (**Figure 1b**, p=0.001). There were significant correlations between improved LRRFS and tumor size <3.5 cm (p=0.034), the absence of cartilage involvement (p=0.007), the absence of ECE (p=0.039), and nodal stage 0-1 (p=0.018) (**Table 3**). There was no difference between the patients who underwent definitive RT in terms of RT indication (**Figure 2b**, p=0.073). Primary treatment modality, tumor size, nodal stage, and cartilage involvement were independent predictors of LRRFS on multivariable analysis (**Table 4**). The 3-y organ preservation rate was 81.5% in the CRT group.

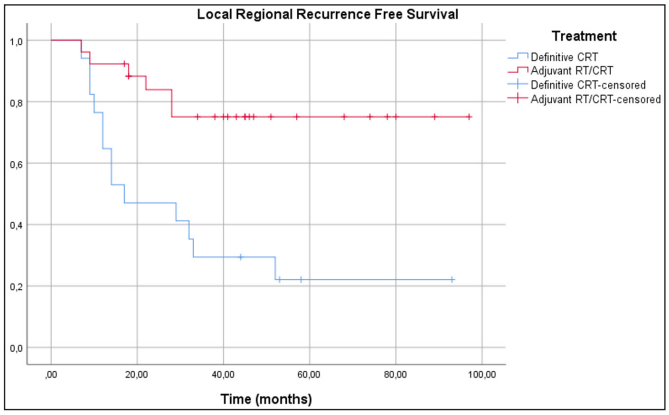

Figure 1b. Kaplan-Meier graph of LRRFS comparing definitive CRT versus adjuvant RT/CRT.

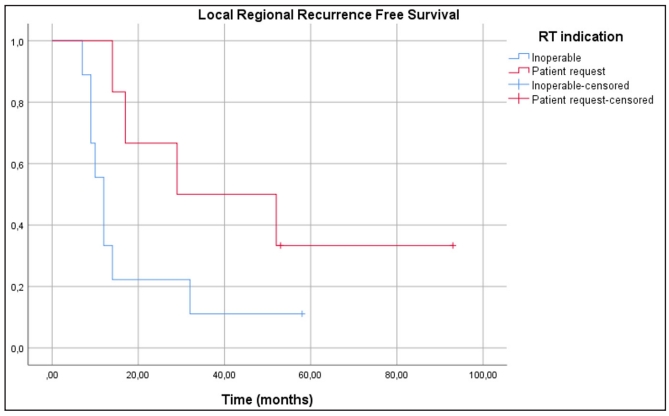

Figure 2b. Kaplan-Meier graph of LRRFS evaluating definitive CRT according to RT indication.

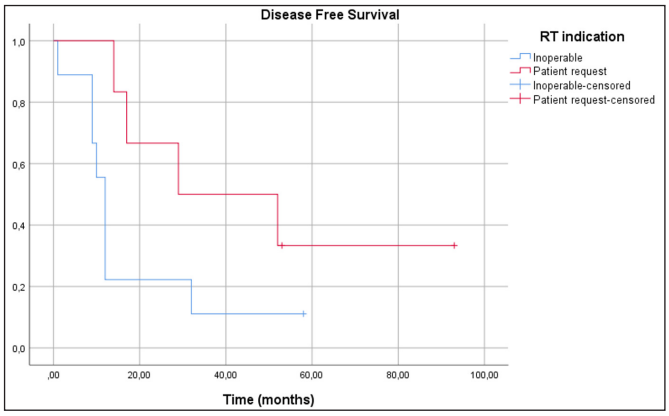

Figure 2c. Kaplan-Meier graph of DFS evaluating definitive CRT according to RT indication.

Distant metastases were seen in 8 individuals over a median 12.5-month period (range: 1-40) after RT. Distant metastases sites were lung (n=8, 100%), and liver (n=1, 12.5%). CT was applied to all patients after metastasis was detected. All patients who developed metastases died within a median of 13 (7-33) months. During the follow-up, lung cancer, a second malignancy, developed in 2 patients (4.34%). The primary malignancies of these patients were under control, and they were being treated for lung cancer.

For the entire cohort, the 5-y DFS was 51.9%, and the mean DFS was 59.43 (HR=6.42, 95% CI: 46.83-72.03) months. A statistically significant difference was found between the treatment groups in terms of 5-y DFS rates, with 75.7% in the adjuvant RT/CRT arm and 22.1% in the CRT arm (**Figure 1c**, p=0.001). There were significant correlations between improved DFS and the tumor size <3.5 cm (p=0.033), the absence of ECE (p=0.014), the absence of cartilage involvement (p=0.009), and nodal stage 0-1 (p=0.013) (**Table 3**). There was no difference between the patients who underwent definitive RT in terms of RT indication (**Figure 2c**, p=0.073). Primary treatment modality, tumor size, nodal stage, stage, cartilage involvement, and ECE (in the postoperative RT group) were independent predictors of LRRFS on multivariable analysis (**Table 4**).

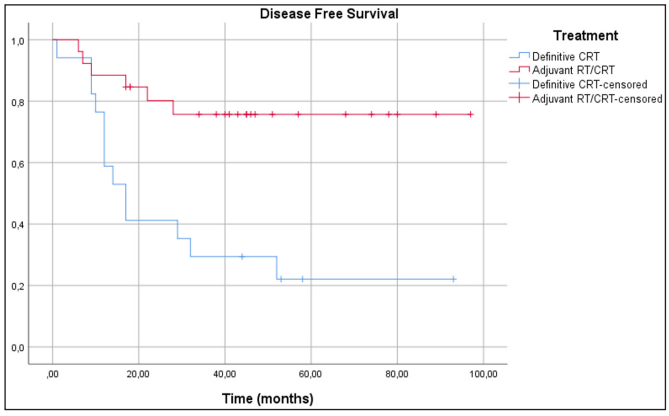

Figure 1c. Kaplan-Meier graph of DFS comparing definitive CRT versus adjuvant RT/CRT.

DISCUSSION

In this study, patients who applied to our clinic with the diagnosis of T4 LC and underwent primary CRT or postoperative RT/CRT were examined to determine survival rates and related factors. According to the analysis, the OS, LRRFS, and DFS rates in T4 patients were considerably lower in the primary CRT group than in the postoperative RT/CRT group. Among the patients who underwent CRT, OS was found to be better in the group applied due to the patient's request compared to the patients referred for RT due to medical or surgical inoperability, and in multivariate analysis, the indication for RT remained an independent predictor of OS. With respect to other clinicopathological factors, age was the only significant factor in OS in multivariate analysis, whereas tumor size, nodal stage, and ECE (in the postoperative RT group, except LRRFS) were linked with OS, LRRFS, and DFS rates.

The Veterans Affairs study, which was published in the early 1990s, was a turning point in the field of LC treatment that prioritized organ preservation.[3] In this trial, 332 patients were randomized to induction CT followed by definitive RT or laryngectomy and postoperative RT. Looking at the 2-y outcomes between the two groups, there was no difference in OS for both arms, with a rate of 68%. The larynx was preserved in 64% of patients who received induction CT followed by RT. Thus, there has been a fundamental change in the management of LC, and it has subsequently become conceivable to discuss laryngeal preservation with promising results in the treatment of patients requiring TL at an advanced stage. When the 2-y results were analyzed in our study, it was found that the survival of the operated patients was quite good compared to definitive CRT (83.4% vs. 47.1%), in contrast to the Veterans Affairs study. However, in the Veterans Affairs study, it was stated that there was no difference in OS between the two groups according to the stages, but

since the survival results for T4 tumors were not given separately, we could not compare them with the results of our study.

The Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC) study, which had the same design as the Veterans Affair study, included only T3 tumors, independent of nodal stage, as a more homogeneous group.[6] About half of the 68 patients were in the induction CT arm, and a statistically significant worsening of OS was reported in the CT arm, with 2-y results of 69% vs. 84%. Comparing the results of this study with our own results would not be helpful as the study design did not include T4 disease, but it is worth noting that survival worsened with nonsurgical treatment across treatment arms.

A decade later, the landmark RTOG 91-11 study highlighted the role of definitive CRT in the management of LC.[4] There was no surgical arm in this study. 547 patients were randomized to induction CT followed by RT, CRT, or RT alone. While no difference was found between the groups in terms of OS, the addition of CT to RT reduced the frequency of distant metastases and contributed to DFS compared to the RT alone arm. The larynx preservation rate was found to be significantly higher in the CRT arm compared to the other two arms (88% vs. 75% vs. 70%). Locoregional control was achieved at the highest rate in the CRT arm (78% vs. 61% vs. 56%). The 5-y OS was 54% in the CRT arm, but it should be kept in mind that T4 tumor rate in this study comprised 9.3% of patients, and only low-volume T4 patients were included in the study. In our study, which included only T4 tumors without any discrimination in terms of tumor volume or spread, the 5-y OS rate in the CRT arm was found to be 35.6%. However, in the subgroup analysis performed according to RT indication, 5-y OS was found to be 66.7% in patients who applied for RT upon the request of the patient, not because of inoperability. According to the long-term results of the RTOG 91-11 study, no survival advantage was observed between the 3 arms, and larynx preservation rates were still found to be highest in the CRT arm.[8] However, it was emphasized that the incidence of deaths not related to cancer due to late side effects was higher in the CRT arm.

In a cohort study examining The National Cancer Data Base data, in the subgroup analysis according to T stages, OS was found to be decreased in those who underwent CRT in T4 disease.[9] The 5-y OS was 57.5% with the upfront TL and 37.8% in the CRT arm. This study showed that there was a difference in OS between the treatment arms for T4 tumors compared to other T stages. Similar to our study, lower OS rates were reported with CRT compared to the surgical arm.

While the efficacy of the organ-preserving approach has been demonstrated in randomized controlled trials, it is frequently reported that this efficacy is lower in the results of observational studies.[3,4,6,9,10] This may be due to the more systematic recruitment of randomized trials. In daily practice, surgical treatment is the preferred method in advanced stages. In particular, patients who cannot tolerate surgery or whose tumor spread is more common and whose operability is difficult are referred for CRT. Among the patient groups compared in observational studies, important factors affecting survival such as decreased performance status and comorbidity may be higher in the CRT group, and treatment responses may be relatively lower in this group. In our study, there was no statistically significant difference between the treatment groups in terms of patient and tumor characteristics; however, it is also noteworthy that OS is better in cases where RT is applied at the request of the patient without inoperable disease.

In the Veterans Affairs study, high local recurrence rates were observed in the induction CT arm, and the rate of salvage laryngectomy was found to be significantly higher for T4 stage compared to other stages (56% vs 29%).[3] In our study, local recurrence was observed in 7 patients in the CRT arm, but salvage surgery was performed in only 2 patients, the 3-y organ preservation rate was 81.5%. We think that the low need for salvage surgery may be due to the fact that 4 of these 7 patients already had distant metastases before and during the detection of local recurrence and that they were receiving CT for this purpose.

Apart from local recurrence, TL may be required in the follow-up period due to long-term side effects after CRT such as laryngeal and/or swallowing dysfunction, long-term tracheotomy, and/or gastrostomy tube dependency resulting from functional failure of the larynx. It has also been reported in important randomized studies that patients who died due to this long-term toxicity were not associated with cancer.[3,4,8] Therefore, some clinicians are concerned about the choice of CRT in advanced stages. In our study, salvage surgery was not required due to the loss of laryngeal function.

Regarding the analyzed variables, age is also known to be a predictor of OS, patients aged <60 years were better OS rates in our results.[11] It is known that there is an important link between nodal stage and survival, and this relationship was also found in our study.[12-14] Tumor size is another important parameter, especially in terms of local control.[15] Increased tumor volume was associated more frequently with local failure. In our study, it was observed that the treatment outcomes were worse for those who were over 3.5 cm. The presence of ECE is clearly known to be associated with a poor prognosis,

requiring an increased radiation dose in areas where it is present and adding CT to RT.[16] Our results were consistent with the literature, and it was determined that the presence of ECE changed the treatment outcomes in operated patients.

The strengths of this study are as follows: Since only T4 tumors were taken in our study, the distribution of patients is more homogeneous. Both groups do not differ in terms of patient characteristics. Thus, more reliable results can be given when making comparisons. However, there are limitations to this study, some inherent to a retrospective study design with inherent confounding factors. In addition, despite the 7-y time period being screened, the number of patients included in the study is relatively low.

CONCLUSION

In T4 disease, the surgical (multimodality treatment) arm had statistically significantly superior results in terms of OS, LRRFS, and DFS compared to the organ-preserving approach with the CRT group. However, it is also noteworthy that OS is better in cases where RT is applied at the request of the patient without inoperable disease. In addition, laryngeal protection was observed to a large extent in the CRT arm.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Samsun University Clinical Researches Ethics Committee (Date: 12.04.2023, Decision No: 2023/7/17).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Long-term outcomes of percutaneous release technique or open for trigger finger in diabetic patients

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ABSTRACT

Aims: Trigger finger is seen more often in diabetic patients and can lead to more serious postoperative complications compared to non-diabetic patients. The aim of this study was to compare the outcomes of open and percutaneous release techniques in diabetic patients.

Methods: This retrospective study included 62 patients who met the study criteria. Of these patients, 32 underwent open release surgery and 30 underwent percutaneous release with an 18-gauge needle. The patients were evaluated retrospectively in respect of the data on first presentation preoperatively and at postoperative follow-up examinations at 3 weeks, 6 months and 1 year. A retrospective examination was made of the demographic data, Visual Analog Scale (VAS) scores preoperatively, at 6 and 12 months postoperatively, recurrence rates at the end of 6 months and 1 year, the Quinnell grading scale at the end of 1 year, wound site infection, tendon damage and neurovascular complications. VAS scores and the Quinnell grading scale were used for clinical evaluation.

Results: The data of a total of 62 patients were statistically analyzed in the study, with 32 (51.6%) in the Open group and 30 (48.4%) in the Percutaneous group. The mean age of the patients was 58.97±7.51 (min-max: 45-72) years. The distributions of trigger finger and Quinnell grading system scores were statistically similar between the groups (P=0.974, P=0.279, respectively). The recurrent triggering rate at the 6th and 12th month was significantly higher in the Percutaneous group (P=0.049, P=0.049, respectively). The average return to work duration in the Percutaneous group (1.70±0.75) was significantly shorter than that in the Open group (3.88±1.21) (P<0.001). Pre-op, Post-op 6th and 12th month VAS scores did not significantly differ between the groups (P=0.466, P=0.356, P=0.175, respectively).

Conclusion: Although satisfactory results were obtained with both percutaneous and open release techniques in the patients with diabetes in this study, the percutaneous release technique was seen to be a method which can be easily performed in an outpatient setting and had fewer complications.

Keywords: Trigger finger, percutaneous, diabetic patients, open surgery, Quinnell grading

INTRODUCTION

Stenosing tenosynovitis which is known as trigger finger (TF) is one of the most frequently seen pathologies of the hand, which causes locking of the finger, swelling, pain and restricted movement. Although the thumb is usually affected, it is also seen in other fingers.[1] The primary cause of TF is thickening of the A1 pulley and entrapment of the flexor tendon by this.[2] TF is seen at a frequency of 2.1% in the non-diabetic healthy population and more often in females aged >30 years, but the lifetime risk in the diabetic population increases up to 8%.[3] The primary treatment option in mild cases with fewer symptoms is conservative treatment, whereas in advanced cases with severe symptoms, different surgical treatments for A1 pulley release are applied.[4]

Many different surgical techniques have been reported and the current most commonly used techniques are open surgery,[5] ultrasound-guided percutaneous release[6,7] and percutaneous release without ultrasound guidance.[8] Complications such as swelling, contracture, pain and infection have been reported at rates of approximately 8% -25% following open release[9] and it has been stated that the incision scar and associated pain can last for months.[10] The percutaneous release technique can be easily performed, provides early functional healing, excellent patient satisfaction and is lower cost.[11,12]

Elssayed et al.[13] reported excellent results at the rate of 97% in a study of patients with TF treated with percutaneous release and no complications such as

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nerve or tendon injury or infection were encountered. It has been stated that the risk of infection development, wound scar and recurrence is 3-fold greater in diabetic patients compared to non-diabetic patients.[14]

The aim of this study was to compare the efficacy of open and percutaneous release techniques in patients with diabetes and to compare the clinical outcomes. The hypothesis of the study was that the recurrence of TF would be lower in patients undergoing open release compared to those undergoing percutaneous release, but there would be more complications.

METHODS

The study was carried out with the permission of Hitit University Non-interventional Reseearches Ethics Committee (Date: 03.07.2023, Decision No: 2023/09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. From a total of 118 patients who presented at the Orthopedics Department of Hitit University and Van Training and Research Hospital between February 2018 and February 2022, this retrospective study included 62 patients who met the study criteria. Of these patients, 32 underwent open release surgery (Group 1) and 30 underwent percutaneous release with an 18-gauge needle (Group 2). All the patients included in the study were aged >18 years, were diabetic, had not responded to at least one month of conservative treatment and were followed up for a minimum of 1 year.

Patients were excluded from the study if they were aged <18 years, not diabetic, had a history of surgery on the same hand, had hypothyroidism, rheumatoid arthritis, tenosynovitis with infection and were using anticoagulants.

The patients were evaluated retrospectively in respect of the data on first presentation preoperatively and at postoperative follow-up examinations at 3 weeks, 6 months and 1 year.

A retrospective examination was made of the demographic data, Visual Analog Scale (VAS) scores preoperatively and at 6 and 12 months postoperatively, recurrence rates at the end of 6 months and 1 year, the Quinnell grading scale at the end of 1 year, wound site infection, tendon damage and neurovascular complications. VAS scores and the Quinnell grading scale were used for clinical evaluation. According to the Quinnell scale, the severity of triggering was evaluated from grades 0-4. Pain was evaluated using the VAS, which measures the severity of pain from 0 (no pain) to 10 (intolerable pain).

Surgical Technique

Open technique: All the open surgery operations were performed in the operating theatre. Throughout the procedure, a pneumatic tourniquet was applied at 250 mmHg pressure. Local anesthesia was provided with an injection of 2% lidocaine. An incision approximately 15 mm wide was performed over the A1 pulley in all the fingers. Blunt dissection was advanced, then with direct imaging, the A1 pulley was cut longitudinally and the range of movement was checked by the finger being moved into flexion and extension. Following irrigation and hemostasis the wound was closed with 4-0 nylon sutures.

Percutaneous technique: All the percutaneous release procedures were performed in an Outpatient Polyclinic room. The surface landmarks were determined as described by Froimson et al.[15] and Fiorini et al.[16] Local anesthesia was provided by infiltration of a 2% lidocaine solution around the nodule from the distal palmar surface of the affected finger using an 18-gauge needle. Then a 18 hypodermic needle was placed at the proximal edge of the A1 pulley and making flexion and extension movements of the finger the needle was seen to move in the same directions and was confirmed to be within the tendon (**Figure 1**). With the sharp edge of the needle, the pulley was cut longitudinally from proximal to distal until a click was felt. To confirm that the pulley had been completely cut, the patient was instructed to move the finger in flexion and extension. Following the procedure, the symptoms of pain and catching should be relieved immediately. If the symptoms were not relieved, the procedure was repeated.

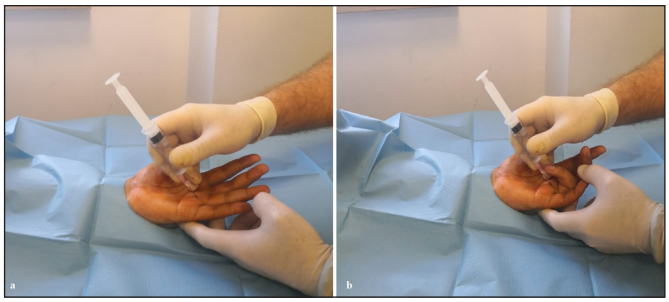

Figure 1. (a) 18 gauge hypodermic needle was placed at the proximal edge of the A1 pulley and (b) clinical picture showing release of A1 pulley

Statistical Analysis

The SPSS software (Version 22, Inc., Chicago, IL, USA, Program license: Hitit University) was used for statistical analyses. The open-source "ggplot2" library in R program was utilized for graph plotting.

Descriptive statistics of categorical variables were reported using numbers and percentages (%), while descriptive statistics of numerical variables were reported as mean ± standard deviation (SD). Normality assumption of numerical data was examined using the Shapiro-Wilk test and graphical approaches (Histogram and Q-Q plot). The assumption of homogeneity of variances was examined using the Levene's test. Relationship investigations between categorical variables were conducted using the chi-square test or Fisher's exact test depending on the sample sizes in cross-tabulation cells. For the comparison of numerical data between independent two groups, the parametric assumption was met, and thus the Student's t-test was employed. For the comparison of more than two related numerical variables, the parametric assumption was satisfied, and therefore the Repeated Measures ANOVA test was used. Following the statistically significant Repeated Measures ANOVA test, Bonferroni post-hoc tests were utilized to determine the time points where the differences occurred. A significance level of P <0.05 was considered statistically significant.

RESULTS

The data of a total of 62 patients were statistically analyzed in the study with 32 (51.6%) in the Open group and 30 (48.4%) in the Percutaneous group. Among the patients, 25.8% (n=16) were male and 74.2% (n=46) were female. The mean age of the patients was 58.97±7.51 (min-max: 45-72) years. The average follow-up duration for all patients was 13.1±1.19 (12-16) months and the average return to work duration was 2.82±1.48 (1-7) weeks.

Statistical findings regarding the comparison of demographic and clinical characteristics between research groups are presented in Table 1. The distributions of gender ratios and sides were statistically similar between the groups (P=0.881, P=0.193, respectively). The distributions of trigger finger and Quinnell grading system scores were statistically similar between the groups (P=0.974, P=0.279, respectively). The recurrent triggering rate at the 6th and 12th month was significantly higher in the Percutaneous group (P=0.049, P=0.049, respectively). The mean ages and follow-up durations did not significantly differ between the groups (P=0.267, P=0.850, respectively). The average return to work duration in the Percutaneous group (1.70±0.75) was significantly shorter than that in the Open group (3.88±1.21) (P<0.001).

Table 1. Statistical findings for the comparison of demographic and clinical characteristics of the patients between study groups

	Groups		P values
	Open (n=32)	Percutaneous (n=30)	
Gender			0.881[a]
Male	8 (25%)	8 (26.7%)	
Female	24 (75%)	22 (73.3%)	
Side			0.193[a]
Right	15 (46.9%)	19 (63.3%)	
Left	17 (53.1%)	11 (36.7%)	
Trigger digit			0.974[a]
Thumb	13 (40.6%)	12 (40%)	
Index	8 (25%)	7 (23.3%)	
Middle	5 (15.6%)	6 (20%)	
Ring	6 (18.8%)	5 (16.7%)	
Recurrent triggering (6 months)			0.049[b]
No	32 (100%)	26 (86.7%)	
Yes	0 (0%)	4 (13.3%)	
Recurrent triggering (12 months)			0.049[b]
No	31 (96.9%)	24 (80%)	
Yes	1 (3.1%)	6 (20%)	
Quinnell grading system (post 12. Months)			0.279[b]
0	24 (75%)	18 (60%)	
1	7 (21.9%)	8 (26.7%)	
3	1 (3.1%)	4 (13.3%)	
Age	60±7.89	57.87±7.04	0.267[c]
Follow-up time (month)	13.13±1.23	13.07±1.17	0.850[c]
Return to work (week)	3.88±1.21	1.70±0.75	<0.001[c]

[a]Chi-square test with n (%), [b]Fisher exact test with n (%), [c]Student's t-test with mean±standard deviation (SD)

Statistical findings regarding the between-group and within-group comparisons of VAS scores are presented in Table 2. Significant decreases in VAS scores were observed at all time points in both groups (P<0.001, P<0.001, respectively). Pre-op, Post-op 6th and 12th month VAS scores did not significantly differ between the groups (P=0.466, P=0.356, P=0.175, respectively). A line graph showing the changes in between-group and within-group VAS scores is presented in Figure 2.

Table 2. Statistical results for the between-group and within-group comparison of VAS scores at different time points.

Groups	VAS			P values (within)	Post-hoc P values
	Pre-op	Post-op 6. month	Post-op 12. month		
Open (n=32)	7.38±0.71	1.88±0.75	0.84±1.05	<0.001[d]	1-2: <0.001 1-3: <0.001 2-3: <0.001
Percutaneous (n=30)	7.5±0.63	2.07±0.87	1.3±1.53	<0.001[d]	1-2: <0.001 1-3: <0.001 2-3: <0.001
P values (between)	0.466[c]	0.356[c]	0.175[c]		

[c]Student's t-test with mean±standard deviation (SD), [d]Repeated Measures ANOVA followed by Bonferroni post-hoc test with mean±SD

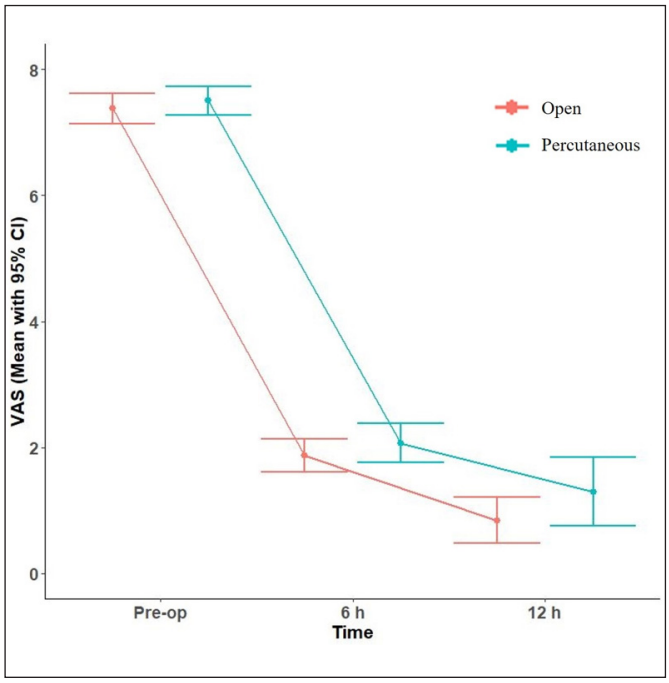

Figure 2. Mean and 95% confidence interval graphs showing the time-dependent variation of repeated measures of VAS scores.

Statistical findings regarding the distributions of complication rates between the groups are presented in Table 3. The rate of scar occurrence was significantly higher in the Open group (P=0.024). The rates of infection and tendon injury were similarly distributed between the groups (P=0.238, P=0.607, respectively). Vascular injury was not observed in either group.

Table 3. Statistical findings for the comparison of complication rates between study groups

		Groups		P values
		Open (n=32)	Percutaneous (n=30)	
Scar	No	26 (81.3%)	30 (100%)	0.024[b]
	Yes	6 (18.7%)	0 (0%)	
Infection	No	29 (90.6%)	30 (100%)	0.238[b]
	Yes	3 (9.4%)	0 (0%)	
Tendon injury	No	31 (96.9%)	28 (93.3%)	0.607[b]
	Yes	1 (3.1%)	2 (6.7%)	
Vascular injury	No	32 (100%)	30 (100%)	-
	Yes	-	-	

bFisher exact test with n (%)

Statistical findings regarding the relationship between trigger finger positions and Quinnell grading system scores are presented in Table 4. No significant relationship was found between trigger finger positions and Quinnell grading system scores in both groups (P=0.631, P=0.952, respectively). A bar graph showing the distributions of Quinnell grading system scores based on trigger finger positions between the research groups is presented in Figure 3.

Table 4. Statistical findings for the relationship between Trigger digit and Quinnell grading system between study groups

Groups	Trigger digit	Quinnell grading system (post 12. months)				P values
		0	1	3	Total	
Open (n=32)						0.631[b]
	Thumb	9 (69.2%)	4 (30.8%)	0 (0%)	13	
	Index	7 (87.5%)	1 (12.5%)	0 (0%)	8	
	Middle	3 (60%)	1 (20%)	1 (20%)	5	
	Ring	5 (83.3%)	1 (16.7%)	0 (0%)	6	
Percutaneous (n=30)						0.952[b]
	Thumb	8 (66.7%)	2 (16.7%)	2 (16.7%)	12	
	Index	4 (57.1%)	2 (28.6%)	1 (14.3%)	7	
	Middle	3 (50%)	2 (33.3%)	1 (16.7%)	6	
	Ring	3 (60%)	2 (40%)	0 (0%)	5	

[b]Fisher exact test with n (%)

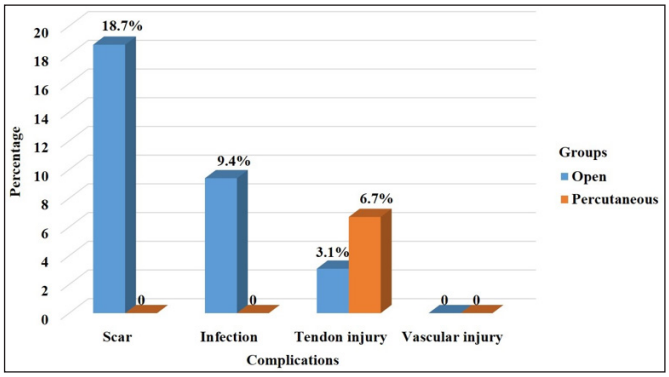

Figure 3. A bar graph showing the distributions of complication rates among the research groups

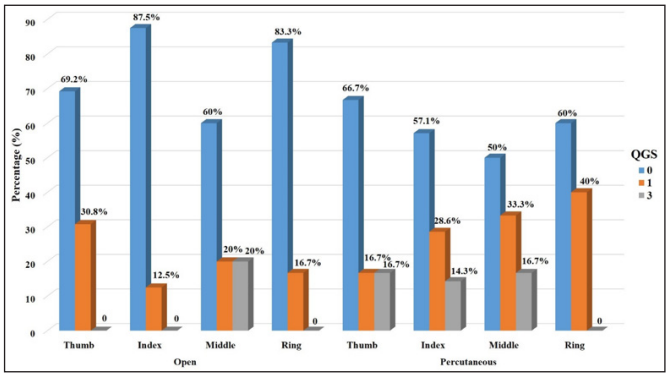

Figure 4. A bar graph showing the distributions of Quinnell grading system scores among the research groups based on fingers.

DISCUSSION

Trigger finger is seen more often in patients with diabetes and can lead to more serious postoperative complications compared to non-diabetic patients. Although there are various surgical treatment options in the treatment of trigger finger (TF), including open release and percutaneous release with and without ultrasound guidance, the optimal surgical treatment remains a matter of debate. Following TF open surgery, complications such as wound scar and associated pain, infection and reflex sympathetic dystrophy may be seen and cause morbidity. As the incidence of the

above-mentioned complications is increased in diabetic patients, DM has been shown to be a poor prognostic factor for surgery.[17] Percutaneous release techniques are applied to reduce all these complications. Instruments such as specially designed knives and hypodermic needles of different sizes are used in percutaneous release procedures. An 18 hypodermic needle was used in this study. To the best of our knowledge, there is no previous study in the literature that has compared open and percutaneous release techniques in diabetic patients and analyzed the complications in the long term.

In a study of diabetic and non-diabetic patients by Huang et al.[14] percutaneous release was performed on 48 diabetic patients and the long-term complications were reported to be persistent pain in the finger in 15 (25%) patients and recurrent TF in 9 (15%). At the end of the first year of another study of 39 patients, there was reported to be recurrent TF in 5 patients.[18] Similarly in the current study, recurrent TF was seen in 6 patients at the end of the first year in the group that underwent open release. In the group applied with the percutaneous release technique, problems such as insufficient release and tendon injuries were reported. In a study of a series of 42 patients, it was stated that there was incomplete release in 3 (6.79%) patients and tendon laceration developed in 6 (13.95%). Tendon injuries were reported at the rate of 6% in a cadaver study that analyzed complications after percutaneous release.[19] Lacerations developing in the tendon can result in rupture in the long term. In the current study, although superficial tendon laceration was seen in 2 (6.7%) patients in the percutaneous group and in 1 (3.1%) patient in the open group, tendon rupture was not observed in any patient at the end of 1 year.

Mishra et al.[20] performed percutaneous release with a hypodermic needle and reported that there was no recurrent TF at the end of the follow-up period of the study, complications were lower in comparison with open surgery and success was obtained at the rate of 95%. In the current study, the success of the release following the A1 pulley incision was confirmed in the percutaneous group by the absence of intraoperative triggering in all the cases and the rate of recurrent TF in the percutaneous group was seen to be similar to that of the above-mentioned studies.

When the percutaneous release technique is performed blind, neurovascular damage is another important complication that can occur. In a study performed with percutaneous release by Alper et al.[18] hypoesthesia was determined in 7 patients. No neurovascular complications were observed in either group in the current study. This difference was thought to be due to the different distribution of thumb and index fingers within the groups and that the nerve in these fingers is closer to the tissue. Previous studies of diabetic patients have reported worse clinical results in respect of recurrent TF rates and patient satisfaction.[21,22] Similarly in the current study, a significantly higher rate of scarring and associated pain was determined in the open group compared to the percutaneous group.

In a prospective study by Gilbert et al.[23] open and percutaneous release techniques were performed on a series of 100 patients, with success reported at the rate of 100% in the percutaneous technique and 98% in the open technique. Permanent pain associated with the formation of excessive scarring was reported in 1 patient in the open group and recurrent TF in 1 patient. The mean time of return to work was reported to be 3.9 days in the percutaneous group and 7.9 days in the open group. Similarly in the current study, the return to work of patients in the percutaneous group was significantly shorter than in the open group.

At the end of the first year of the current study, the VAS scores were found to be mean 1.3 in the percutaneous group and 0.8 in the open group (**Figure 2**). Quinnells grade 0 was determined in 75% of the patients in the open group and in 60% of the percutaneous group at the end of the first year. Scarring developed in 6 patients in the open group and no scar was seen in any patient in the percutaneous group. The patients who developed scarring received physiotherapy and NSAID treatment and there was no requirement for additional surgery.

Limitations of this study can be considered to be the retrospective design of the study and the relatively low number of patients.

CONCLUSION

Although satisfactory results were obtained with both percutaneous and open release techniques in the patients with diabetes in this study, the percutaneous release technique was seen to be a method which can be easily performed in an outpatient setting and had fewer complications. In addition to the negligible recurrence rate of the percutaneous technique compared to open release, it also has the significant advantages of lower cost, an earlier return to work and fewer complaints of pain associated with scarring.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Non-interventional Researches Ethics Committee (Date: 03.07.2023, Decision No: 2023/09).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Comparison of 99mTc-HMPAO-labeled leukocyte scintigraphy findings with systemic inflammatory markers

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ABSTRACT

Aims: Technetium-99m-hexamethylpropylene amine oxime (99mTc-HMPAO) labeled leukocyte scintigraphy is frequently used for infection imaging. The systemic immune-inflammation index is a new marker. In this study, we aim to investigate the relationship between 99mTc-HMPAO-labeled leukocyte scintigraphy findings and systemic inflammatory markers such as Neutrophil/lymphocyte ratios (NLR) and Platelet lymphocyte ratio (PLR) and systemic immune-inflammation index (SII).

Methods: Patients who underwent 99mTc-HMPAO-labeled leukocyte scintigraphy between 2014 and 2020 due to suspected infection such as diabetic foot infection or prosthesis infection vs. in any part of the body were included in our study. In addition, a negative control group consisting of 19 normal subjects who had no leukocyte scintigraphy and had hemogram examination was added to the study. Cases with findings consistent with infection in labeled leukocyte scintigraphy and infectious symptoms in this area of involvement in the clinical examination were considered as the positive group. The data were evaluated with the SPSS 23.0 program.

Results: Our study included 36 patients (28 males,8 females, mean age: 59.7). The mean SII was 1526±787 x109 cells/L in patients with positive findings in leukocyte scintigraphy that might be compatible with infection, while it was 1025 ± 370 x109 cells/L in patients who did not (p=0.017). The mean PLR was 183.95±68.30 in patients with positive findings in leukocyte scintigraphy that might be compatible with infection, while it was 145.81±58.30 in patients who did not (p=0.102). The mean NLR was 4.82±1.91 in patients with positive findings on leukocyte scintigraphy that might be compatible with infection, while it was 4.15±1.40 in patients who did not (p=0.181). While the negative control group and the patients who were considered positive in leukocyte scintigraphy were compared; a statistically significant difference was found between SII, NLR and PLR values. When the relationship between SII was evaluated, the mean SII was 1526±787 x109 cells/L in patients with involvement that may be compatible with infection in leukocyte scintigraphy, while it was 762±224 x109 cells/L in the negative control group (p<0.05). While the relationship between PLR was evaluated, the mean PLR was 183.95±68.30 in patients with involvement that might be compatible with infection in leukocyte scintigraphy, while it was 100.67±26.18 in the negative control group (p<0.05). When the relationship between NLR was evaluated, the mean NLR was 4.82±1.91 in patients with involvement that might be compatible with infection in leukocyte scintigraphy, while it was 3.11±0.85 in the negative control group (p<0.05).

Conclusion: When labeled leukocyte scintigraphy and systemic inflammatory markers were compared, there was a statistically significant relationship between the presence of infection in scintigraphy and SII, but the relationship with NLR and PLR were not statistically significant. When the negative control group and the patients who were considered positive in leukocyte scintigraphy were compared; a statistically significant difference was found between SII, NLR and PLR values. For this reason, we think that SII, NLR and PLR may be useful markers for diagnosis confirmation in centers that can't perform radiolabeled infection imaging.

Keywords: Leukocyte scintigraphy, Infection, SII, NLR, PLR, systemic immune-inflammation index

This study was presented as an oral presentation at the 33rd National Nuclear Medicine Congress held online on 28-29 May 2021 in Turkey.

INTRODUCTION

Blood consists of plasma and cells. Plasma contains protein, amino acids, enzymes, antibodies, lipids, salts, carbohydrates, hormones and gases. Blood cells are divided into three erythrocytes, leukocytes and platelets. Leukocytes are major cellular components of the inflammatory and immune response that play a protective role against infections and neoplasia and also help repair damaged tissue. 55-65% of peripheral leukocytes are neutrophils, 3% are eosinophils, 0.5% are basophils, 25-35% are lymphocytes, and 3-7% are monocytes. In normal times, only 2-3% of leukocytes are found in the circulating blood. The remainder of the leukocytes, attached to the vascular endothelial tissue, are found in the bone marrow, liver, lung, spleen, gastrointestinal tract, and oropharynx. In the presence of an acute inflammatory condition, these cells accumulate in this region by performing chemotaxis and diapedesis. In the chronic phase, lymphocytes migrate to the inflammatory region.[1]

Radiolabeled leukocyte scintigraphy, which is based on the detection of areas where leukocytes accumulate by labeling them with radioactive substances that

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emit gamma radiation, is frequently used for infection imaging. One of the radiopharmaceuticals used for this purpose is 99mTc HMPAO. 99mTc-HMPAO, a cerebral perfusion agent, enters the cell by passive diffusion. Hexamethylpropyleneamine oxime is labeled with 99mTc and is used in brain perfusion imaging and labeled leukocyte scintigraphy. It has a lipophilic structure, but it reacts with glutathione in the cell and turns into a hydrophilic structure and binds to the nucleus and mitochondria. Once injected i.v. to the patient, radiolabeled leukocyte migrates rapidly to the lungs and, if not damaged, proceeds to the liver, spleen and the reticuloendothelial system, including bone marrow. Approximately 1 hour after injection, labeled cells further migrate to bone marrow and, in case of an infection, to the infected tissue due to chemotactic attraction caused by biofilm and its soluble products.[2] The sensitivity, specificity and accuracy values of leukocyte scintigraphy show different results within the infection groups. There are different values for prosthetic infections and osteomyelitis. In the study by Love et al.[3] they investigated the diagnostic accuracy of labeled lymphocyte scintigraphy in 59 patients with painful, failed, lower extremity joint prostheses, In this study 40 hip and 19 knees who underwent (18)F-FDG, labeled leukocyte, and bone marrow imaging, and had histopathologic and microbiologic confirmation of the final diagnosis, the sensitivity, specificity, and accuracy of labeled leukocyte/marrow imaging were 100%, 91%, and 95%, respectively. With the addition of F-18 FDG PET/CT examination to the marked leukocyte scintigraphy for the diagnosis of osteomyelitis, the sensitivity increases to 90%.[4] Autologous labeled leukocytes are very specific as they accumulate after adhering to the vascular endothelium by active migration across the basement membrane into infected tissue.[5] HMPAO, a lipophilic chelator, has high efficacy in labeling leukocytes with Tc-99m.[6] The neutrophil/lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are used to evaluate systemic inflammation. However, these two inflammatory markers allow an evaluation based on neutrophil and lymphocyte counts. Abnormal increases in inflammatory blood cell parameters including neutrophil count, the neutrophil-to-lymphocyte ratio[7], [8], the monocyte-to-lymphocyte ratio[9], and the platelet-to-lymphocyte ratio[10,11] serve as simple markers of inflammation. But these biomarkers involve only two types of immune-inflammatory cells and might not accurately reflect the inflammation status. The marker called systemic immune-inflammation index is a new prognostic marker that allows an evaluation based on neutrophil, platelet and lymphocyte counts.[12,13] All three parameters in this marker can be easily calculated from routine complete blood counts in peripheral blood.

In this study, we aimed to investigate the relationship between 99mTc-HMPAO-labeled leukocyte scintigraphy findings and systemic inflammatory markers such as NLR, PLR and SII.

METHODS

Ethical Approval

This study was approved by the Sancaktepe Şehit Prof. Dr. İlhan Varank Training And Research Hospital Non-interventional Clinical Researches Ethics Committee of (Date: 2023-03-08, No: 37). Medical records, scintigraphy findings and other data of the patients were evaluated retrospectively. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Patients who underwent 99mTc-HMPAO-labeled leukocyte scintigraphy between 2014 and 2020 due to suspected infection such as diabetic foot infection or prosthesis infection vs. in any part of the body were included in our study. Patients under antibiotic treatment and patients who do not have a recent hemogram were not included in our study. Cases with findings consistent with infection in labeled leukocyte scintigraphy and infectious symptoms in this area of involvement in the clinical examination were considered as the positive group. However, clinical follow-up was not performed for patients. In addition, a negative control group consisting of 20 normal subjects who had no leukocyte scintigraphy and had hemogram examination was added to the study and included in the statistical evaluations.

Radiolabeling of Leukocytes and Scintigraphic Imaging

Labeling of leukocytes in the blood with 99mTc-HMPAO is a complex process consisting of several steps. To have sufficient leukocytes in the labeling, 30-50 cc of blood from the patient is taken into a tube containing Anticoagulant Citrate Dextrose (ACD, consisting of 0.73 g of anhydrous citric acid, 2.2 g of sodium citrate dihydrate and 2.45 g of dextrose monohydrate in 100 ml of water for injection), which has anticoagulant properties. By adding 6% hetastarch to this tube, erythrocytes are precipitated. The red blood cells remain in the pelleted part by forming a precipitate with the starch solution. The supernatant contains white blood cells. This part is taken with the help of a butterfly needle. Platelets and proteins are removed from the blood and centrifuged for 5 minutes at 300-350 g centrifuge speed. White blood cells accumulate at the bottom of the tube. The plasma is separated and purified by centrifugation, and leukocyte isolation is completed. Isotonic NaCl solution is added to the white blood cells and incubated with 99mTc-HMPAO for 10 min at room temperature.

99mTc-HMPAO enters into leukocytes and is labeled by passive diffusion. The purification process is done by centrifugation at 150 g for 5 min of 99mTc-HMPAO-leukocyte suspension, to remove 99mTc-HMPAO that is not labeled with leukocytes and free 99mTc in the medium. The obtained radiopharmaceutical is injected into the patient through the peripheral vein.

After the injection, whole-body scintigraphic imaging was performed at the 1st hour, and static scintigraphic imaging was performed from the relevant regions at the 4th and 24th hours. All data acquisition was performed with a double-head SPECT system (DDD-Quantum Cam, Denmark) equipped with a low-energy, high-resolution collimator and a 140 keV energy photopeak. Visual and semiquantitative interpretations were based on the current guidelines of the European Association of Nuclear Medicine and performed by nuclear medicine physicians without knowing the results of the corresponding hemogram results. Patients without significant pathological accumulation of increased activity during labeled leukocyte scintigraphy were considered to be negative for leukocyte scintigraphy (**Figure 1**). Visual interpretation defined a case as positive for infection when there was a clear increase of radiotracer uptake (in terms of intensity or size) in the late images compared with the early images (**Figure 2A**, **2B**, **2C**).

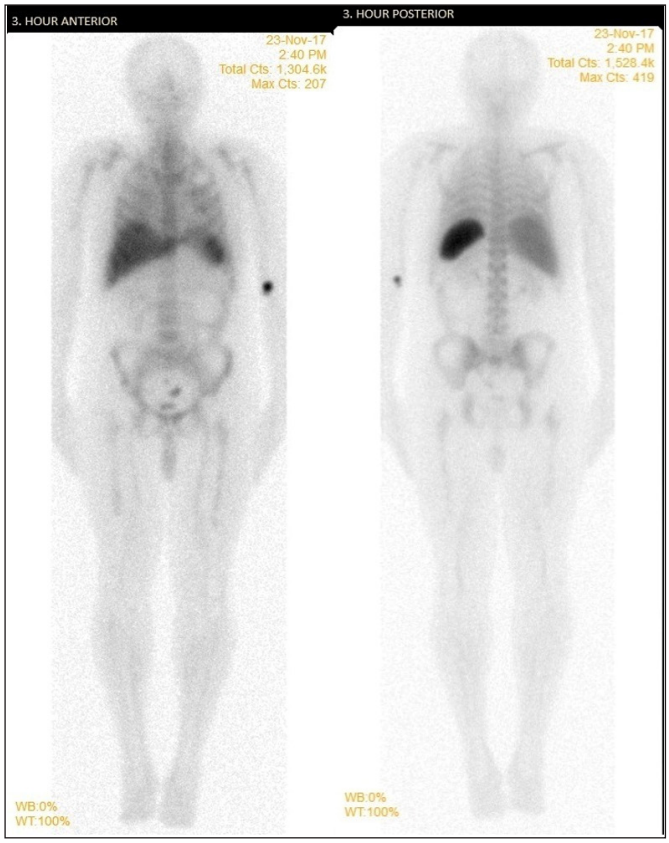

Figure 1: Tc-99m HMPAO labeled leukocyte scintigraphy images of the patient who did not have pathological findings compatible with infection (SII value was 544, leukocyte count was 5660, NLR value was 3.16, and PLR value was 96).

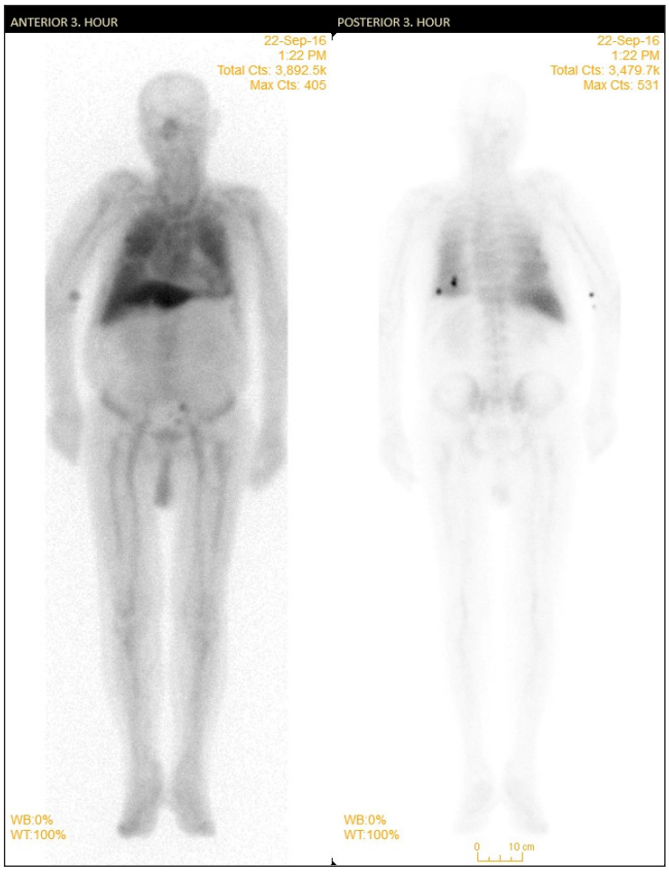

Figure 2A: Whole body images of the Tc-99m HMPAO labeled leukocyte scintigraphy taken 3 hours after the radiopharmaceutical injection of the patient referred for suspected diabetic foot infection (SII value was 1658, leukocyte count was 9310, NLR value was 9.70, and PLR value was 178).

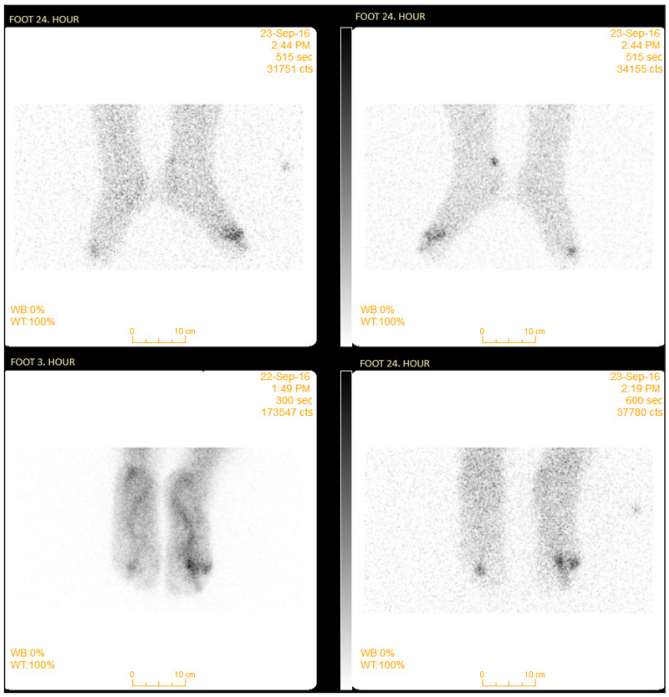

Figure 2B: Static spot foot images of the Tc-99m HMPAO labeled leukocyte scintigraphy taken 4 hours and 24 hours after the radiopharmaceutical injection of the patient referred for suspected diabetic foot infection (SII value was 1658, leukocyte count was 9310, NLR value was 9.70, and PLR value was 178).

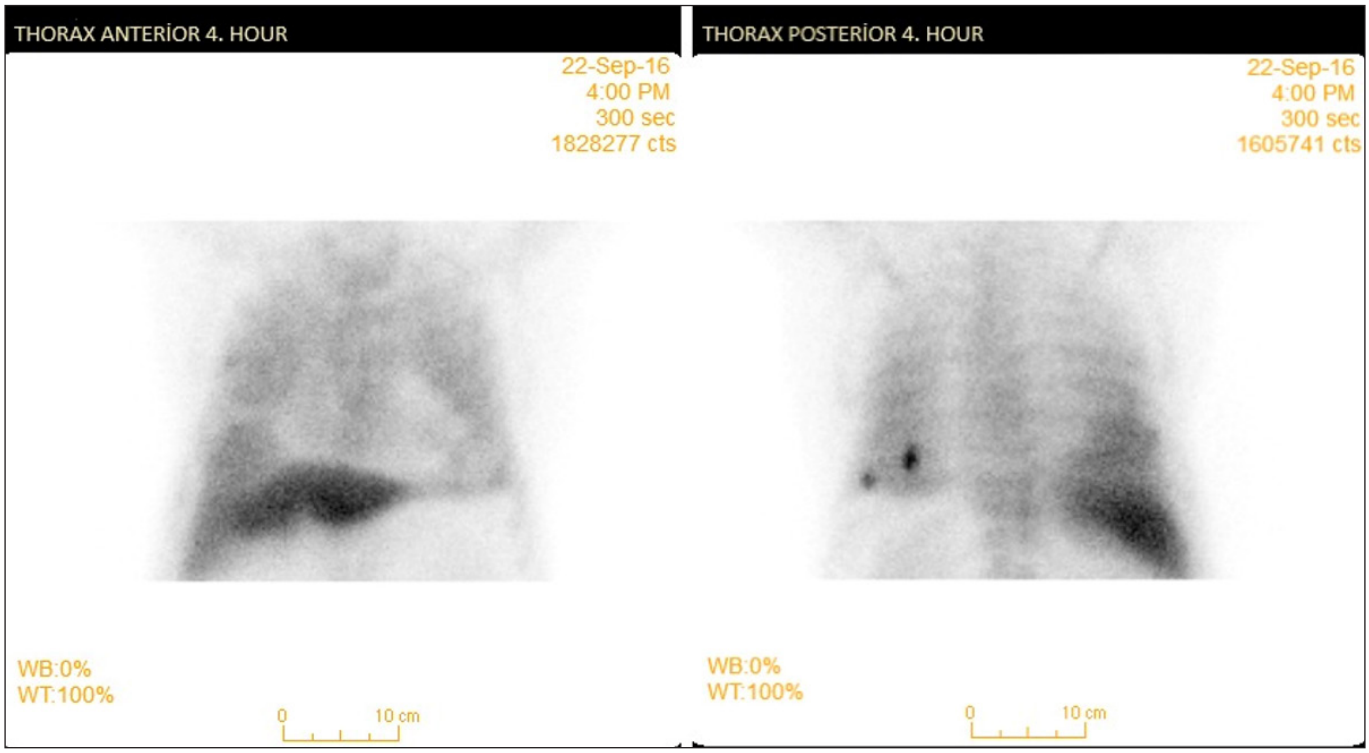

Figure 2C: Static spot thorax images of the Tc-99m HMPAO labeled leukocyte scintigraphy taken 4 hours after the radiopharmaceutical injection of the patient referred for suspected diabetic foot infection (SII value was 1658, leukocyte count was 9310, NLR value was 9.70, and PLR value was 178).

Blood Count

Complete blood count analysis was performed using an autoanalyzer (Sysmex XN1000, Japan). C-reactive protein (CRP) measurements were performed using the turbidimetric method (Roche Cobas c702, Mannheim, Germany). The normal CRP values in our laboratory are <5 mg/L. Platelet count was measured using an automatic blood counter. The SII value was obtained by multiplying the absolute platelet count in the hemogram with the absolute neutrophil count and dividing this value by the absolute lymphocyte value (SII = (platelet count × neutrophil count) / lymphocyte count). NLR was calculated by dividing the absolute neutrophil count by the absolute number of lymphocytes, and PLR was calculated by dividing the absolute platelet count by the absolute number of lymphocytes. The data were evaluated with the SPSS 23.0 program.

Statistical Analysis

Analysis was performed by using the SPSS Statistical Software program (SPSS version 23.0, SPSS Inc., Chicago). A p-value of <0.05 was considered statistically significant during the tests. During the comparison of categorical and numerical data, Independent Student's t-Test was used for normally distributed data, and Mann Whitney U test was used for the analysis of non-normally distributed data. All the continuous variables of the study were described by descriptive statistics such as mean, median, and standard deviation (SD). Categorical variables were described by frequency and percentages.

RESULTS

In our study, there are 36 patients who had labeled leukocyte scintigraphy for infection imaging. Of the patients included in the study, 8 (22.2%) were female and 28 (77.8%) were male (age range: 19-88; mean: 59.7). There were 19 people in the negative control group. Of the people included in the negative control group, 8 (42%) were female and 11 (58%) were male. There was an average of 4 days between scintigraphic imaging and hemogram examinations (range 0-10 days). The mean 99mTc-HMPAO radiopharmaceutical dose given to the patients was 10.03±4.06 mCi.

When the patients who were reported as positive and negative for leukocyte scintigraphy were evaluated among themselves; there was a statistically significant relationship between the presence/absence of findings compatible with infection in leukocyte scintigraphy and platelet count, hemoglobin level, SII and erythrocyte sedimentation rate, no significant relationship was found between WBC, NLR, lymphocyte count, PLR and CRP. When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and SII was evaluated, the mean SII was 1526±787 $\times 10^9$ cells/L in patients with involvement that may be compatible with infection in scintigraphy, while it was 1025±370 $\times 10^9$ cells/L in patients without (p=0.017). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and PLR was evaluated, the mean PLR was

183.95±68.30 in patients with involvement that might be compatible with infection in scintigraphy, while it was 145.81±58.30 in patients without (p=0.102). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and NLR was evaluated, the mean NLR was 4.82±1.91 in patients with involvement that might be compatible with infection in scintigraphy, while it was 4.15±1.40 in patients without (p=0.181). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and WBC was evaluated, the mean WBC was 8.43±2.69 $\times 10^9$/L in patients with involvement that may be compatible with infection in scintigraphy, while it was 7.31±2.07 $\times 10^9$/L in patients without (p=0.170). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and the platelet count was evaluated, the mean platelet count was 321±98 $\times 10^9$/L in the patients with involvement that might be compatible with the infection in the scintigraphy, while it was 251±63 $\times 10^9$/L in the patients without it (p=0.045). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and hemoglobin level was evaluated, the mean hemoglobin level was 12.4±1.9 g/dL in patients with uptake in scintigraphy that might be compatible with infection, while it was 13.55±1.67 g/dL in patients without (p=0.049). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and CRP level was evaluated, the mean CRP level was 48.3 mg/L in patients with uptake that might be compatible with infection in scintigraphy, while it was 31.1 mg/L in patients without (p=0.057). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and erythrocyte sedimentation rate was evaluated, the mean erythrocyte sedimentation rate (ESR) was 60.8 mm/hr in patients with involvement that may be compatible with infection in scintigraphy, while it was 29.15 mm/hr in patients without (p=0.003) (**Table 1**).

Table 1. Comparison of SII, NLR and PLR values in the patients who had positive leukocyte scintigraphy and had negative leukocyte scintigraphy

	Leukocyte Scintigraphy		p
	Positive	Negative	
SII	1526±787	1025 ± 370	0.017
NLR	4.82±1.91	4.15±1.40	0,181
PLR	183.95±68.30	145.81±58.30	0,102
WBC	8.43±2.69	7.31±2.07	0.170
PLT	321±98	251±63	0.045
HGB	12.4±1.9	13.55±1.67	0.049
CRP	48.3	31.1	0.057
Erythrocyte sedimentation rate	60.8	29.15	0.003

When the negative control group and the patients who were considered positive in leukocyte scintigraphy were compared; a statistically significant difference was found between SII, NLR and PLR values. When the relationship between SII was evaluated, the mean SII was 1526±787 $\times 10^9$ cells/L in patients with involvement that may be compatible with infection in scintigraphy, while it was 762±224 $\times 10^9$ cells/L in negative control group (p<0.05). When the relationship between PLR was evaluated, the mean PLR was 183.95±68.30 in patients with involvement that might be compatible with infection in scintigraphy, while it was 100.67±26.18 in negative control group (p<0.05). When the relationship between NLR was evaluated, the mean NLR was 4.82±1.91 in patients with involvement that might be compatible with infection in scintigraphy, while it was 3.11±0.85 in negative control group (p<0.05) (**Table 2**).

Table 2. Comparison of SII, NLR and PLR values in the patients who had positive leukocyte scintigraphy and the normal negative control group who had no leukocyte scintigraphy.

	Patients with positive leukocyte Scintigraphy	Negative Control Group	p
SII	1526±787	762±224	<0.05
NLR	4.82±1.91	3,11±0,85	<0.05
PLR	183.95±68.30	100.67±26,18	<0.05
WBC	8.43±2.69	7.66±1.74	>0.05
PLT	321±98	249±60	<0.05
HGB	12.4±1.9	13.9±1.2	<0.05

DISCUSSION

99mTc-HMPAO-labeled leukocyte scintigraphy is a noninvasive imaging method with high diagnostic accuracy and is highly preferred in infection imaging due to its high specificity and sensitivity. In their studies, Govaert et al.[14] obtained 0.79 sensitivity, 0.97 specificity in fracture-related infections, Granados et al.[15] obtained 0.72 sensitivity, 0.95 specificity in periprosthetic infections. It is based on the principle that the blood taken from the patient is injected into the patient by separating the white blood cells (leukocytes, WBC) and marking them with 99mTc-HMPAO and imaging on gamma cameras. The main laboratory tests for the diagnosis of infection are erythrocyte sedimentation rate, CRP and leukocyte count. These tests are non-specific indicators of inflammation. In recent studies, NLR, PLR and SII, which are novel inflammatory markers, have been considered useful indicators for the diagnosis and prognosis of various infectious diseases. In our study, there was a significant relationship between ESR and the presence of infection.

In the study by Şener et al.[16], it was investigated whether the systemic immune-inflammation index is a reliable parameter that can be used in the diagnosis of acute

appendicitis and they stated that systemic immune-inflammation index may be used to promote the diagnosis of acute appendicitis and may reduce the need for radiation exposure and diagnostic imaging tests such as contrast-enhanced abdominal computed tomography. And also they claimed that it can also be used to differentiate between complicated and non-complicated acute appendicitis cases.

The study by Ozer et al.[17] aimed to investigate the clinical and diagnostic significance of inflammatory markers, including the systemic immune-inflammation index (SII) and erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin (PCT) to differentiate osteomyelitis and cellulitis. In conclusion, given that the patients with osteomyelitis had much higher ESR, CRP, PCT, and SII levels combined with the fact that SII is a low-cost and easy-to-measure index, suggests that the same may serve as an effective and novel marker alternative to other inflammatory markers for predicting diabetic foot osteomyelitis. A significant portion of the patients in our study group consisted of labeled leukocyte scintigraphy performed due to diabetic foot infection. Also, in our study when presence/absence of findings consistent with infection in leukocyte scintigraphy and SII was evaluated, the mean SII was higher in patients with involvement that may be compatible with infection in scintigraphy.

The study by Wang et al.[18] aimed to compare the predictive value of the NLR, SII, SIRI and PLR for stroke-associated pneumonia in patients with intracerebral hemorrhage to determine their application potential in the early identification of the severity of pneumonia. Among the four indexes, the NLR was the best predictor for stroke-associated pneumonia occurrence and a poor outcome at discharge in intracerebral hemorrhage patients. It can therefore be used for the early identification of severe stroke-associated pneumonia and to predict ICU admission. Although it was not statistically significant in our study, when the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and NLR was evaluated, the mean NLR was higher in patients with involvement that might be compatible with infection in scintigraphy.

In the study conducted by Carpio-Orantes et al.[19], in which the usability of NLR, PLR and SII indexes were investigated to determine the severity of COVID-19, it was stated that these parameters could be used to determine the severity of COVID-19. Asik,[20] researched the usability of NLR and PLR for diagnosis in patients with urinary tract infections and during his study, he found that NLR and PLR values were higher in patients with urinary tract infections compared to the healthy volunteer control group and suggested that they can be used as inflammatory markers in patients with infection. In the study conducted by Yang et al.[21] in which he investigated the diagnostic and predictive roles of NLR and PLR in COVID-19 patients, he stated that NLR could be considered as an independent biomarker to predict poor clinical outcomes. Although it was not statistically significant in our study, when the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and PLR was evaluated, the mean PLR was higher in patients with involvement that might be compatible with infection in scintigraphy.

CONCLUSION

99mTc-HMPAO-labeled leukocyte scintigraphy is a noninvasive method with high diagnostic accuracy used in the investigation of infection/inflammation focus. The main laboratory tests for the diagnosis of infection are erythrocyte sedimentation rate, CRP and leukocyte count. These tests are non-specific indicators of inflammation. In the first part of our study, patients who had leukocyte scintigraphy were compared. According to the first part of our study with a limited number of patients, when labeled leukocyte scintigraphy and systemic inflammatory markers were compared, there was a statistically significant relationship between the presence of infection in scintigraphy and SII, platelet count, hemoglobin level and erythrocyte sedimentation rate, while the relationship with NLR, PLR, WBC and CRP were not statistically significant. In the second part of our study, the patients who had leukocyte scintigraphy were compared with the normal negative control group who had no leukocyte scintigraphy. When the negative control group and the patients who were considered positive in leukocyte scintigraphy were compared; a statistically significant difference was found between SII, NLR and PLR values. For this reason, we think that SII, NLR and PLR may be useful markers for diagnosis confirmation in centers that cannot perform radiolabeled infection imaging.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 08.03.2023, Decision No: 37)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Is borderline oligohydramnios a problem at term pregnancy? a prospective study of a tertiary hospital

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ABSTRACT

Aims: The objective of this study is to conduct a comparative analysis and ascertain the perinatal and early postnatal outcomes in term pregnant women who have a borderline amniotic fluid index (AFI) in comparison to those with a normal AFI.

Methods: This prospective study was conducted on 376 pregnant women of 37-42 weeks gestational age. Ultrasound evaluation was performed, and the AFI was calculated. Borderline and normal AFI were defined as 5.1 < AFI < 8 cm and 8.1 < AFI < 24 cm, respectively. Age, body mass index, gestational age at delivery, gravida, and parity were compared between the borderline and normal AFI groups, patient demographics, obstetric data, and information on delivery complications data were recorded. Newly born babies received a thorough physical evaluation and were followed up for two months by a neonatologist. Umbilical artery pH, birth weight, admission to neonatal intensive care unit (NICU), neonatal complications were also reported.

Results: There were 202 patients in the borderline AFI group and 174 patients in the normal AFI group. There was no statistically significant difference between groups in terms of normal delivery, operative vaginal delivery, elective cesarean delivery, or emergency cesarean delivery (p=0.088). Apgar score at 5 minutes, umbilical artery pH value, birth weight, admission to the NICU, small for gestational age, and cesarean delivery for non-reassuring fetal heart rate testing were not statistically different between the groups (p=0.139, p=0.644, p=0.790, p=0.317, and p=0.16, respectively)

Conclusion: Our study indicates that borderline oligohydramnios does not have an adverse effect on perinatal or early postnatal outcomes in term pregnancy.

Keywords: Oligohydramnios, term pregnancy, perinatal outcomes, postnatal outcomes

INTRODUCTION

Pregnancy management often consists of a series of predictions and decisions for both the mother and fetus. Some parameters can be used to predict the risks potentially encountered by the fetus and assess the length of pregnancy or the time of delivery. Amniotic fluid is one of these parameters and is an essential predictor of both pregnancy and fetal outcomes.[1,2] Therefore, changes in the volume of amniotic fluid should be monitored.

The most common method for assessing the volume of amniotic fluid is the amniotic fluid index (AFI). The volume of amniotic fluid varies based on the gestational week. Oligohydramnios can be defined as a volume of amniotic fluid <5% for gestational age, AFI <5 cm.[3] Borderline oligohydramnios is defined as an amniotic fluid index between 5 and 8 cm.[4,5] In addition, some authors have defined an AFI 5-10 cm as borderline.[6,7] However, the findings of these studies indicated a similar propensity associated with borderline AFI using both definitions.

Oligohydramnios has been associated with adverse outcomes, such as neonatal intensive care unit (NICU) admission, meconium aspiration syndrome, 5-minute Apgar score <7, low cord gas pH, low birth weight, and respiratory distress syndrome.[3] The results of borderline oligohydramnios are controversial. Although it has been associated with meconium staining, fetal hypoxia, and operative delivery in some sources, some studies have found the opposite results.[8-12] However, the management and risks in borderline oligohydramnios remain unclear, especially in term pregnancies.

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This study aims to compare and determine differences in the perinatal and early postnatal outcomes of pregnant women with borderline AFI with those with normal AFI.

METHODS

This prospective study was approved by Health Sciences University Adana Numune Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 11.03.2015, Decision No: 123), and written informed consent was obtained from all participants. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study population was selected from pregnant women who were admitted to our clinic. During the routine antenatal examination of all volunteers, a total of 378 pregnant volunteers with an uncomplicated singleton pregnancy at a gestational age of 37-42 weeks were included in the study between July 2015 and April 2016.

Patients were excluded if they had any of the following: preeclampsia, gestational diabetes, genetic disease or fetal anomaly, fetal growth restriction, maternal systemic disease, and membrane rupture before ultrasound examination. Ultrasound evaluation was performed with a 10-MHz Nemio XG system (Toshiba Medical Systems GmbH) by two obstetricians with at least five years of experience. The AFI was determined using the four-quadrant amniotic fluid measurement technique as defined by Phelan et al.[11] Borderline and normal AFI were defined as 5.1<AFI<8 cm and 8.1<AFI<24 cm, respectively.

The patients were followed up with an ultrasound examination every week until delivery. Patients in whom the AFI decreased to <5 cm during the follow-up were excluded from the study. We recorded data, including patient demographics, obstetric data, and information on delivery complications.

All patients' delivery techniques were documented. Patients were divided into four groups according to their delivery method: normal vaginal delivery, operative vaginal delivery, elective cesarean delivery, or emergency cesarean delivery. Elective cesarean delivery was applied to patients who had a previous cesarean section and refused vaginal delivery after previous cesarean section.

Adverse perinatal and early postnatal outcomes were recorded. Prematurity, Apgar score 5 min <7, cesarean delivery for non-reassuring fetal heart rate, transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), meconium-stained amniotic fluid, meconium aspiration syndrome, admission to the neonatal intensive care unit (NICU) and length of stay on the NICU, hyperbilirubinemia, intubation, hypoxic-ischemic encephalopathy (HIE), necrotizing enterocolitis and neonatal death were evaluated.

Statistical Analysis

Data were analyzed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA). The normality of data was investigated using the Shapiro Wilk test, and values were expressed as mean±standard deviation, median, or n (%). Parametric comparisons were made using a student t-test for continuous variables, and nonparametric comparisons were made using the Mann-Whitney U test. For qualitative data, we used the $\chi 2$ test or Fisher's exact test as appropriate to test statistical significance and $p<0.05$ value was considered statistically significant.

RESULTS

We enrolled 202 patients in the borderline AFI group and 176 patients in the normal AFI group. Table 1 shows the demographic and obstetric characteristics of patients. Age, body mass index, abnormal first trimester screening results, gravida, parity, gestational week of ultrasound examination for AFI, AFI, and gestational age at delivery were compared between the borderline and normal AFI groups. There were no statistically significant differences between the groups ($p>0.05$).

Table 1. Demographic and obstetric characteristics of patients

	Borderline AFI (n=202)	Normal AFI (n=176)	P value
Age (years)	28.79±5.66	29.16±5.41	0.650
BMI (kg/m²)	30.58±5.02	30.16±4.61	0.557
Gravida	2.85±1.38	3.17±1.46	0.136
Parity	1.66±1.19	1.81±1.05	0.356
Abnormal first trimester screening	None	None	-
Gestational week of ultrasound examination for AFI	38.2±0.876	37.6±0.725	0.062
AFI (cm)	6.72±0.98	10.67±2.94	<0.005*
GA at delivery (weeks)	38.65±1.2	38.8±0.67	0.333

Each characteristic was compared between the borderline and normal AFI groups. Data are presented as mean±SD. GA, gestational age; AFI, amniotic fluid index, BMI, body mass index. A p-value <0.05 is considered significant. t-test and chi-square test were used to compare qualitative and quantitative variables.

Table 2 presents perinatal outcomes in patients with borderline and normal AFI. Apgar score <7 at 5 minutes, UA pH value, birth weight, admission to the NICU, small for gestational age, meconium-stained amniotic fluid and cesarean delivery for non-reassuring fetal heart rate testing were not statistically different between the groups (p=0,812, p=0.139, p=0.644, p=0.790, p=0.317, and p=0.16, p=0,162 respectively). None of the newborns developed neonatal hyperbilirubinemia, hypoxic-ischemic encephalopathy, respiratory distress syndrome, or necrotizing enterocolitis.

Table 2. Perinatal outcomes in patients with borderline and normal amniotic fluid index.

	Borderline AFI (n=202)	Normal AFI (n=176)	P value
APGAR score <7 at 5 minutes	8 (4%)	6 (3.4%)	0.812
Umbilical artery pH	7.32±0.04	7.33±0.03	0.139
Birth weight (g)	3264.40±393.44	3292.87±448.76	0.644
NICU admission	8 (4%)	4 (2.3%)	0.790
SGA	4 (2%)	6 (3%)	0.317
Meconium-stained amniotic fluid	2 (1%)	2 (1.1%)	0.162
Cesarean delivery for non-reassuring fetal heart rate	2 (1%)	2 (1.1%)	0.162

Each perinatal outcome was compared between the borderline and normal AFI groups. Data are presented as n (%) as appropriate. NICU, neonatal intensive care unit; SGA, small for gestational age.
A p-value <0.05 is considered significant. t-test and chi-square test were used to compare qualitative and quantitative variables.

Table 3 compares the delivery types in patients with borderline and normal AFI. There was no statistically significant difference between groups in terms of normal delivery, operative vaginal delivery, elective cesarean delivery, or emergency cesarean delivery (p=0.088, p=0.262, p=0.754, p=0.823, p=0.088, respectively).

Table 3. Delivery type in patients with borderline and normal amniotic fluid index.

	Borderline AFI (n=202)	Normal AFI (n=176)	P value
Vaginal delivery	120 (59%)	135 (6.9%)	0.088
Operative vaginal delivery	6 (3%)	2 (1.1%)	0.262
Elective cesarean delivery	62 (30.6%)	28 (78.2%)	0.754
Emergency cesarean delivery	14 (6.9%)	13 (14.9%)	0.823

Each characteristic was compared between the borderline and normal AFI groups. Data are presented as n (%) as appropriate. xA p-value <0.05 is considered significant. t-test and chi-square test were used to compare qualitative and quantitative variables.

DISCUSSION

The present study has demonstrated that borderline amniotic fluid index (AFI) in an uncomplicated term pregnancy is not associated with an elevated risk of adverse perinatal and early postnatal outcomes. The present study had a prospective design. We found no statistically significant difference between the borderline AFI and normal AFI groups in terms of Apgar score <7 at 5 minutes, UA pH, birth weight, NICU admission, small for gestational age, meconium-stained amniotic fluid, and cesarean delivery for non-reassuring heart rate. There were no neonatal complications (neonatal hyperbilirubinemia, hypoxic-ischemic encephalopathy, respiratory distress syndrome, necrotizing enterocolitis). Six newborns followed up in the NICU were discharged with full recovery by one month.

There are limited studies in the literature to assess borderline AFI and adverse perinatal and early postnatal outcomes. According to some authors, borderline oligohydramnios can elicit perinatal and early postnatal complications included fetal distress, 5-minute Apgar score <7, meconium-stained amniotic fluid, Neonatal Intensive Care Unit (NICU) admission.[13] In a retrospective study with a large number of preterm pregnancies, fetal growth restriction, major malformation, and preterm delivery were more common in pregnant women with borderline oligohydramnios than those with normal AFI. However, the rate of stillbirths was higher in those with oligohydramnios than in those with borderline oligohydramnios.[14] In a comprehensive study involving 430 patients, researchers followed late preterm patients until birth and evaluated borderline AFI and normal AFI. They found that only fetal renal artery PI was significantly lower in the borderline AFI group. There was no difference in parameters such as adverse perinatal outcome (prematurity, 5-minute Apgar score <7, respiratory distress syndrome, etc.). The authors stated that borderline AFI does not increase the risk of adverse outcomes in uncomplicated late preterm pregnancies.[4] Lekkala et.al.[15] reported that, gestational age, induction, Apgar scores were not different between borderline and normal AFI groups. Nevertheless, the borderline AFI group had a higher rate of fetal distress, IUGR, and meconium-stained amniotic fluid. Gumus et al.[6] demonstrated an increased risk with borderline oligohydramnios for meconium-stained amniotic fluid, preterm birth, intrauterine growth restriction (IUGR), and frequency of NICU admission, which included preeclampsia, hypertension, and IUGR pregnancies.

In our study, the absence of additional conditions such as preeclampsia, gestational diabetes, and hypertension might have enabled us to evaluate the results of borderline oligohydramnios more specifically. We excluded from our study patients with preeclampsia, gestational diabetes, genetic disease or fetal anomaly, preterm and post-term pregnancy, and maternal systemic disease (diabetes mellitus, systemic lupus erythematosus, thyroid disease, etc.). This may explain the difference between our results and findings from some previous studies.

The study design and gestational age of the study population are also crucial in interpreting the results. The present study included only term pregnancies. When we focus on term pregnancies in this context, in a study including pregnant women at 37-42 weeks of gestation, gestational age and birth weight was low in the borderline group. The rates of cesarean delivery and cesarean section due to fetal distress were higher in the borderline AFI group than in the normal AFI group. However, the ratio of meconium staining, 5-minute Apgar score <7, UA pH <7, and admission

rate to the NICU were not statistically different between the groups.16 Vennila et al.[13] reported that; borderline oligohydramnios is associated with increased incidence of meconium staining of amniotic fluid, fetal distress, and cesarean delivery. Soo Ran Choi et al.[17] reported borderline AFI in uncomplicated term pregnancy was not associated with adverse perinatal outcomes.

When we evaluate the effects of borderline oligohydramnios on the delivery, Rathod et al.[10] compared the process of labor induction and delivery mode between the borderline AFI and normal AFI groups. In their study, more borderline oligohydramnios cases had meconium-stained fluid in labor than normal AFI cases (p=0.048) but no statistically significant difference between groups in terms of perinatal outcomes (Apgar score <7 at 1 and 5 minutes, birth weight, or NICU admission rate (p=0.234, 0.834, 0.481, and 0.810, respectively) and cesarean for non-reassuring fetal heart rate. Some studies were consistent with this data and reported no difference in the mode of delivery.[4,18] But others reported the opposite.[13-15,19,20] In our study, there was no difference in meconium-stained fluid, delivery mode or cesarean rate.

In another study, the degree of oligohydramnios was arbitrarily classified into mild (AFI=41-50 mm), moderate (AFI=21-40 mm) and severe (AFI=0-20 mm). They found that Low-risk pregnancies with isolated severe oligohydramnios at term have a higher tendency toward non-reassuring fetal monitoring requiring prompt delivery and adverse neonatal outcomes.[21] Clinicians should be careful about AFI measurements below 5 cm, as there was no statistically significant relationship between 5-8 cm AFI measurements and > 8 cm AFI measurements in our study.

Limitations

The results of studies on borderline oligohydramnios in the literature, which includes different gestational ages and different designs, still make this issue important. One of the limitations of the current study was the relatively small number of participants, and further research with larger sample size is needed in this field.

CONCLUSION

The present study suggests that in term pregnancies, borderline AFI is not associated with adverse perinatal and early postnatal outcomes. This issue will be further clarified by studies with a larger number of cases. However, given the present data, increased antepartum surveillance for these patients is not necessary.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Adana Numune Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 11.03.2015, Decision No: 123)

Informed Consent: Written informed consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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A noteworthy prognostic marker in extensive small cell lung cancer: lymphocyte/C-reactive protein ratio

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ABSTRACT

Aims: We aimed to investigate the pre-treatment prognostic significance of lymphocyte/C-Reactive protein ratio (LCR), one of the inflammatory factors, in patients with extensive-stage small cell lung cancer (SCLC).

Methods: Medical records of 514 patients who were diagnosed with extensive-stage SCLC between 2010 and 2020 were examined retrospectively. LCR was calculated using the blood test results prior to chemotherapy.

Results: The mean survival time for extensive-stage SCLC is 6 months (5.3-6.7). A statistically significant difference exists between limited and extensive stages in terms of median overall survival (OS) ($p<0.001$). The baseline LCR value of the patients was determined as 0.5 (0-311). LCR exerts a statistically significant effect on overall survival (0.025). Every 1 unit increase in LCR reduces death by 1.004 times.

Conclusion: Pre-treatment LCR value can be used as an independent prognostic parameter associated with mean survival in extensive SCLC.

Keywords: Small cell lung cancer, lymphocyte/CRP ratio, prognostic factor, survival

INTRODUCTION

Small cell lung cancer (SCLC) constitutes approximately 15% of all lung cancers with the worst histological course.[1] 60-70% of these carcinomas are extensive-stage, and the median overall survival (OS) is averagely 6 to 8 months.[2] There is still no standardized prognostic marker that can determine survival,[3] therefore there is a need for new markers. Studies show a strong link between systemic inflammation and cancer. Inflammation paves the way for cancer development and effects all stages of tumor formation.[4] Several cytokines and mediators produced secondary to inflammation may increase cell proliferation, invasion, and metastasis development.[5] Systemic immune-inflammation index (SII), prognostic nutrition index (PNI) and neutrophil/lymphocyte ratio (NLR), which are thought to reflect systemic inflammation, have been associated with prognosis in many solid organ malignancies, including esophageal and lung cancer.[6] Systemic inflammation response index (SIRI), another inflammatory indicator, has been defined as a prognostic and predictive factor for various types of cancer, including pancreatic cancer and non-small cell lung cancer (NSCLC).[7,8] The ratio of hemoglobin (Hb) and red cell distribution width (RDW) (HRR) are novel prognostic markers in SCLC, and in this study, it has been shown that each unit increase in HRR reduces death and survival by 1.6 times.[9] Another study in NSCLC showed that low HRR was associated with shorter survival.[10] Recently, the lymphocyte-to-C-reactive protein ratio (LCR), a novel marker, was shown to exert prognostic significance for lung cancer.[11] Another study reported the prognostic significance of many inflammatory markers in extensive-stage SCLC.[12] A decrease in lymphocyte/monocyte ratio (LMR) was found to be a poor prognostic indicator in extensive-stage SCLC.[13] Despite growing evidence of the impact of these inflammation-based scores on the prognosis of SCLC patients, there is limited information on the prognostic significance of the novel parameters. The aim of this study was to determine whether the easily measurable LCR value is an independent prognostic factor for OS, with the number of patients that may be sufficient considering this deficiency.

METHODS

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki and approved by Ankara Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.03.2023, Decision No: 2012-KAEK-15/2676) for studies involving humans and the study was

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designed retrospectively, no written informed consent form was obtained from patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

Extensive-stage SCLC patients diagnosed between January 2010 and January 2020 at Chest Diseases Clinics were included in the study. Inclusion criteria: (i) histopathologically diagnosed extensive-stage SCLC; (ii) adequate imaging data for computed tomography (CT), magnetic resonance imaging device (MRI), and PET-CT tumor staging; (iii) no previous antitumor therapy (including radiotherapy, chemotherapy, immunotherapy and targeted therapy); (iv) routine blood and blood biochemistry findings based on hospital laboratory test results. Exclusion criteria: (i) patients younger than 18 years of age; (ii) patients with limited stage SCLC and non-small cell lung carcinoma (NSCLC) confined to one lung and regional lymph nodes only and can be included in a safe radiotherapy field; (iii) patients with secondary carcinoma; (iv) patients with concomitant infections, inflammatory diseases, lymphoproliferative diseases.

1039 SCLC patients were screened. A total of 514 patients were included in the study after the exclusion of 199 patients without PET-CT results and 326 patients with limited stage.

Clinical Data

Clinical data such as age, gender, smoking history, staging, treatment regimens (chemotherapy, radiotherapy, adjuvant therapy, neoadjuvant therapy, operation), and pre-treatment LCR values were recorded. LCR value was calculated using CBC values as follows: Lymphocyte x 1000/ CRP (mg/l).

Tumor Staging

Tumor staging was performed based on the eighth edition of the staging criteria published by the International Association for the Study of Lung Cancer.14

Observation Indicators

Median overall survival (OS) was defined as the time interval between initiation of treatment and final follow-up and/or death.

Statistical Analysis

Descriptive statistics were used to express continuous variables (mean, standard deviation, minimum, median, maximum).

Conformity of continuous variables to normal distribution was analyzed by the Shapiro-Wilk test.

Overall survival was examined by Kaplan-Meier method.

The effect of blood parameters on survival was examined by Cox Regression analysis.

Measurement of blood parameters and predictive power of progression and death were examined by ROC analysis.

The value of statistical significance was determined as 0.05. The analyses were performed using the MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; 2021) Program.

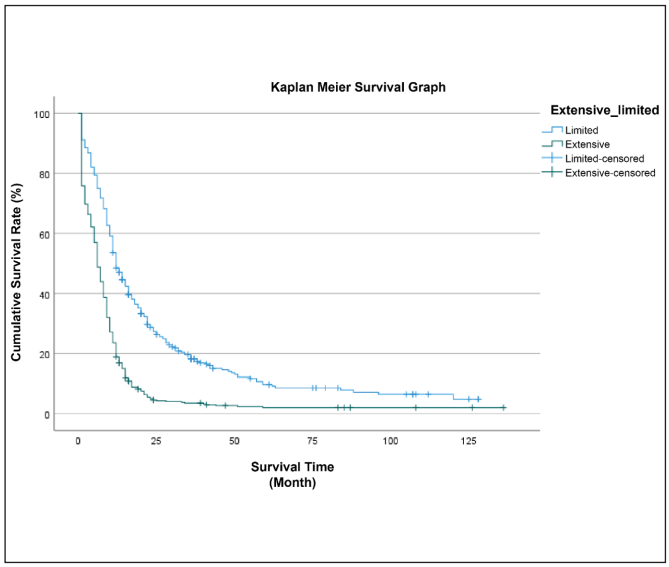
RESULTS

514 patients were included in the study. Of the patients participating in the study, 461 (89.6%) were male and 53 (10.3%) were female. The mean age was 62.7. 211 (41%) patients had a history of smoking. 326 patients (38.9%) were in the limited stage and 514 patients (61.1%) were in the extensive stage. 111 (13.2%) patients had bone metastasis, 22 (2.6%) lung, 16 (1.9%) liver, 25 (3%) adrenal gland, 10 (1.2%) brain, and 328 (39.1%) more than two organs. The clinical characteristics of the participating patients are listed in Table 1. The mean survival time for extensive-stage SCLC is 6 months (5.3-6.7). A statistically significant difference exists between limited and extensive disease stages in terms of OS ($p<0.001$) (Figure 1). The initial LCR value of the patients was 0.5 (0-361), and there was a statistical difference between the limited and extensive disease groups. NLR value was 3.7 (0.8-157.1) and CRP/Alb value was 0.6 (0-65.7) in the extensive stage group while statistical significance was noted in the limited stage group. Laboratory parameters are shown in Table 2. LCR exerts a statistically significant effect on overall survival in the extensive group. A 1-unit increase in LCR reduces death by 1.004 times (Table 3). As shown by the ROC analysis, LCR was not found to be effective in predicting death, and the baseline cut-off value could not be determined (Figure 2).

Table 1. Demographic data and laboratory parameters

	n (%)
Gender	
Male	461(89.6)
Female	53 (10.3)
Age (years)	62.7
Smoking	211 (41)
Smoking consumption amount (pack/year)	48.9 (+25.5)*
Disease Stage:	
Limited Stage	326 (38.9)
Extensive Stage	514 (61.1)
Metastasis localizations:	
Bone	111 (13.2)
Opposite Lung	22 (2.6)
Liver	16 (1.9)
Surrenal	25 (3)
Brain	10 (1.2)
> Two organs	328 (39.1)

*: Mean ± SD



	Median	St. Error	95% Confidence Interval-Lower limit	95% Confidence Interval-Upper limit
Limited	12.0	0.7	10.54	13.46
Extensive	6	0.3	5.3	6.7

Figure 1. Effect of limited/extensive involvement on overall survival

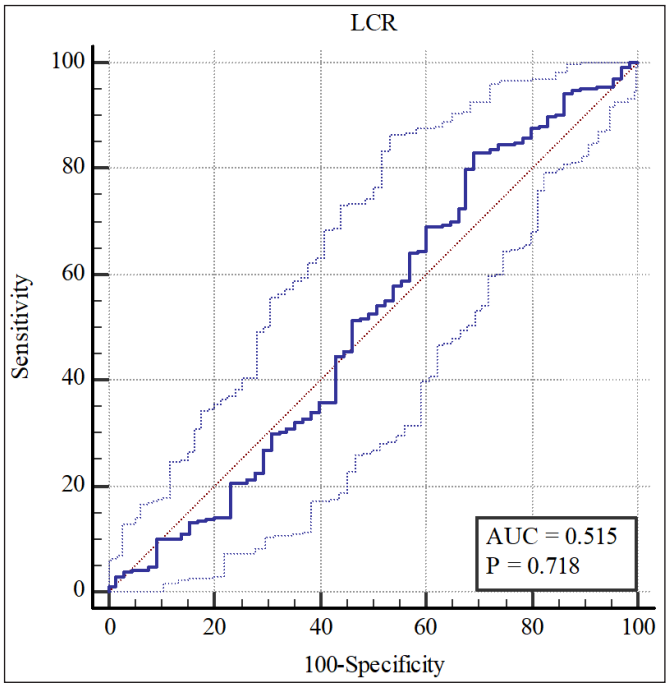


Figure 2: LCR ROC analysis graph

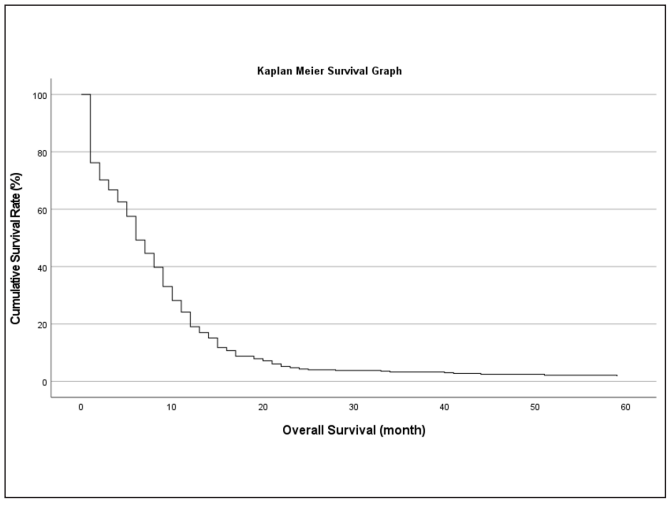
Table 2. Evaluation of Parameters by Limited and Extentive Stages

	Limited	Extensive	p
LCR	0.7 (0-361)	0.5 (0-311)	0.002
NLR	3.1 (12684.7-687.7)	3.7 (0.8-157.1)	<0.001
Platelet/Alb.	57.7 (3.2-219.1)	62.2 (1.0-44.6)	0.337
PLR	18.2 (2.6-42.9)	18.9 (2.3-60.8)	0.542
CRP/Alb.	0.4 (0-14.7)	0.6 (0-65.7)	<0.001
HRR	1 (0.4-1.4)	1 (0.3-1.4)	0.533

CRP: C-reactive protein, HRR: Hemoglobin/Red cell distribution width ratio LCR: lymphocyte/CRP ratio, NLR: neutrophil/lymphocyte ratio PLR: Platelet/lymphocyte ratio

Table 3. Effect of LCR Values on Overall Survival in the Extensive Group

	p	HR	95% CI
LCR	0.025	0.996	0.993-1.00



DISCUSSION

In small cell lung cancer, survival time has not been improved due to the lack of novel treatment options and simple and effective parameters for assessing prognosis. Extensive-stage SCLC especially displays an aggressive course, and the median overall survival (OS) is averagely 6 to 8 months.[2] OS was 6 months in our study, which was consistent with the literature.

In a study by Yuan He et al.[11] consistent with the findings of previous studies, LCR was determined as an independent prognostic marker for both PFS and OS, whereas decreased LCR was found to be a poor prognostic marker. A study by Yılmaz H et al.[12] which is the first publication in our country demonstrating the prognostic significance of novel inflammatory markers in extensive small cell lung cancer, showed that LCR is an independent prognostic marker for both PFS and OS. In this study, PFS ($p < 0.001$) and OS ($p < 0.001$) were found to be longer in the patient group with high LCR than in the low LCR group. In our study, the LCR value was not found to be significant in predicting death, and the basal cut-off value could not be determined. Again, in the study conducted by Iriagac et al.[13] in Turkey, OS was 8.78 (1.07-54.80) months and PFS was 5.6 (1.07-44.03) months in extensive-stage SCLC patients. In their study, PFS was 4.5 months and OS was 7.5 months in the low lymphocyte/monocyte ratio (LMR) group, whereas the median PFS was 6.5 months and OS 10.1 months in the high LMR group. It was thought that high LMR might have good prognostic value for survival (HR: 0.54 95% CI 0.38-0.77. p=0.001). In our study, LCR exerted

a statistically significant effect on overall survival in the extensive group. It was determined that every 1-unit increase in LCR reduced the death by 1.004 times, however, the LCR value was not found to be effective in predicting death according to the result of the ROC analysis, and the lower and upper group analysis could not be performed since the basal cut-off value could not be determined.

CONCLUSION

In this study, we revealed that LCR was associated with overall survival in extensive-stage SCLC patients, which suggests that LCR can be used as a prognostic marker.

Nonetheless, the fact that it is a single-center retrospective study and there is no standard cut-off value that can be compared is among the limitations of our study. Prospective studies including all factors affecting LCR value are needed to reveal the relationship of LCR with OS as an independent factor.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.03.2023, Decision No: 2012-KAEK-15/2676).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Investigation of the synovial fluid pro-inflammatory cytokines and clinical findings in disc displacements of TMJ

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ABSTRACT

Aims: Temporomandibular disorders (TMD) are common musculoskeletal disease that affects the soft tissues and bone structures of the temporomandibular joint (TMJ). Inflammatory mediators play a critical role in the etiology of TMD by affecting various molecular mechanisms. This study aims to investigate the effect of pro-inflammatory cytokines on TMJ internal derangements and evaluate the relationship between clinical features.

Methods: Patients who underwent arthrocentesis because of TMD were included in this study. Patients were divided into 2 groups according to anterior disc displacement with reduction (Group 1) and without reduction (Group 2). Clinical findings before and after the arthrocentesis were evaluated retrospectively. Synovial fluid TNF-α, IL-1β, and IL-6 levels were analyzed with the ELISA method.

Results: A total of 28 patients were included, with 15 patients in Group 1 and 13 patients in Group 2. All patients were female with an average age of 30.75±14.9. The average pre-operative pain score was 6.6±1.95 in all patients. After the arthrocentesis, the average pain score was 2.0 (1.0 - 2.5) and the difference was significant ($p<0.001$). Group 1 have a higher maximum mouth opening (MMO) than Group 2 preoperatively and the difference was statistically significant ($p=0.013$). The difference in synovial fluid cytokine levels was not statistically significant between groups. There was no statistically significant correlation between cytokines and clinical findings.

Conclusion: Arthrocentesis is beneficial for reducing joint pain in patients with TMJ internal derangements. Pro-inflammatory cytokine levels are similar in TMJs with disc displacement with and without reduction.

Keywords: Temporomandibular joint, TMJ, inflammatory, cytokine, synovial fluid

INTRODUCTION

Temporomandibular disorders (TMD) are a type of musculoskeletal disease that affects the soft tissues and bone structures of the temporomandibular joint (TMJ) and proceeds with functional abnormalities including muscle/joint discomfort and restricted jaw movement.[1] Internal derangements and osteoarthritis, characterized by the degenerations in cartilage and bone tissues, represents the most common forms of TMD. It has been observed that inflammatory mediators such as various cytokines or chemokines are released in the synovial fluid of patients with TMJ internal derangement or osteoarthritis, and there is also evidence of persistent inflammation and infiltration of inflammatory cells playing a critical role in the breakdown of articular structures within the synovium of osteoarthritis patients.[2,3] Hence, it becomes essential to assess the potential roles of cytokines and other mediators in illuminating the cellular and molecular events in the pathophysiology of TMJ internal derangement and osteoarthritis.

Treatment of TMD is based on conservative and surgical interventions. Patient education, dietary modifications, medical care, physical therapy, intraoral splint applications, and psychological therapy procedures are among the conservative treatment methods. Minimally invasive procedures are used when conservative treatment fails and clinical complaints continue. Intra-articular injections, intra-muscular injections, arthrocentesis, and arthroscopic lysis and lavage are minimally invasive techniques.[4] In the treatment of

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TMD, the physician should choose the least invasive and most effective treatment method for the patient, as repeated intra-articular interventions may reduce the chances of success. Therefore, arthrocentesis can be considered as the initial treatment option for patients who do not respond to conservative treatment. If arthrocentesis does not achieve success, arthroscopic surgery or other surgical interventions should be considered.[5] Synovial fluid samples taken during lavage can be used to evaluate TMJ disease and provide detailed information about inflammatory components in synovial fluid.[6] After the identification of arachidonic acid metabolites in painful TMJ, many other studies have been reported which provide an opportunity to evaluate composition changes to potentially diagnose and monitor response to treatment of TMJ disorders.[7,8] The first studies comparing cytokine levels in patients with internal derangement involving degenerative changes to healthy controls were published in the 1990s, and it was reported that patients had higher levels of TNF-α and IL-1β in synovial fluid compared to controls.[9] Another study reported elevated levels of IL-6 in 72% of patients with degenerative joint disease.[10] These studies demonstrate the role of TNF-α, IL-1β, and IL-6 in synovial inflammation. This study aims to investigate the effect of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) on TMJ internal derangements and evaluate the relationship between clinical features.

METHODS

The study was carried out with the permission of Erciyes University, Clinical Researches Ethics Committee (Date: 2019, Decision No: 556), and carried out at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry. All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki.

Patients who presented with TMJ complaints had a diagnosis, treatment, and follow-up were retrospectively reviewed for their suitability to participate in the study. Inclusion criteria for the study follow 1) Patients with complaints such as pain, tenderness, joint noises, and limited mouth opening in TMJ and clinically diagnosed with both anterior disc displacement with reduction (ADDwR) and anterior disc displacement without reduction (ADDwoR) according to the diagnostic criteria for temporomandibular disorders (DC/TMD) 2) Patients who received conservative treatment for TMD but did not show improvement in clinical findings, leading to the application of arthrocentesis 3) Patients from whom synovial fluid samples were obtained during arthrocentesis and with complete and well-documented medical records. Clinical diagnosis was also confirmed with magnetic resonance images (MRI). Patients with a history of trauma to the TMJ area and patients who underwent arthrocentesis and/or surgical interventions were excluded from the study. The medical records of patients who received treatment for TMJ internal problems were retrospectively reviewed between the years 2005 and 2019. Patients were divided into two groups according to the diagnosis. Group 1 consisted of patients with ADDwR and Group 2 consisted of patients with ADDwoR. For the study, the included patients' demographic data, dental history, diagnosis, clinical examination findings before and after arthrocentesis including maximum mouth openings (MMO), visual analog scale scores (VAS: 0-10), and follow-up information were gathered. Synovial fluid samples were used in the study from patients who underwent arthrocentesis procedures following the method described by Nitzan.11 During the arthrocentesis procedure, samples were collected by injecting and aspirating 2 ml of normal saline or Ringer's lactate solution into the upper joint space ten times. The levels of TNF-α, IL-1β, and IL-6 in synovial fluids were analyzed with ELISA (Enzyme-Linked Immuno Sorbent Assay) method. Findings were compared between groups.

Statistical Analysis

The statistical analysis of the data was performed using the Turcosa statistical software (Turcosa Analitik Ltd. Şti., www.turcosa.com.tr). The normal distribution of the data was evaluated using histograms, q-q plots, and the Shapiro-Wilk test. The homogeneity of variance was tested using the Levene test. For group comparisons, an independent two-sample t-test was used for parametric data, while the Mann-Whitney U test was used for non-parametric data. Within-group comparisons were conducted using a dependent two-sample t-test or Wilcoxon test. The data were expressed as mean ± standard deviation, median (1st and 3rd quartiles), or frequency (percentage). All analyses were performed with a statistical significance level of $p<0.05$, indicating statistical significance at a 95% confidence interval.

RESULTS

Preoperative Assessments

In the study, a total of 28 patients were included, with 15 patients in Group 1 and 13 patients in Group 2. All patients in the study were female with an average age of 30.75±14.9. The mean age was 30±16.4 in Group 1 and 31.6±13.5 in Group 2 ($p=0.781$). The average VAS score was 6.6±1.95 in all patients. Average MMO was measured 35.6± 5.8 mm in all patients before arthrocentesis.

Pre-operative VAS scores were found 6.8±1.4 in Group 1 and 6.3±2.4 in Group 2 and the difference was not significant (p=0.460). Maximum mouth openings (MMO) were compared and Group 1 have a higher MMO (38.86±5.98 mm) than Group 2 (33.53±4.31) and the difference was statistically significant (p=0.013).

Postoperative Outcomes

After the arthrocentesis procedure, the average VAS score was 2.0 (1.0 - 2.5) and MMO was 36.6±7.6 mm in all patients. The post-operative VAS score was statistically significantly lower (p<0.001). However, post-operative MMO was not statistically significant from preoperative values in all patients (p=0.316).

Post-operative VAS score was found 1.0 (1-2) in Group 1 and 2.0 (1-6) in Group 2 (p=0.164). Post-operative MMO was 38.3±8.06 in Group 1 and 35.5± 7.4 in Group 2 but the difference was not statistically significant (p=0.411). All data were shown in Table 1.

Table 1. Comparison of clinical findings between groups

	Pre-op VAS	Pre-op MMO(mm)	Post-op VAS	Post-op MMO(mm)
Group 1	6.8±1.4	38.86±5.98	1.0 (1-2)	38.3±8.06
Group 2	6.3±2.4	33.53±4.31	2.0 (1-6)	35.5± 7.4
P value	0.460*	0.013*	0.164†	0.411*

VAS: Visual Analog Scale, MMO: Maximum mouth opening, Data are given as median (1st-3rd quartiles) and mean ± standard deviation, *:Student t test, †: Mann Whitney U test

Synovial Fluid Analysis

Synovial fluid TNF-α, IL-1β, and IL-6 levels were compared according to the groups. The average levels were 148.75±22.5, 788.46±207.7 and 83.86±18.0 in Group 1 and 146.41±27.3, 735.53±172.6 and 90.0±16.9 in Group 2 respectively. The difference of synovial fluid cytokine levels were not statistically significant between groups (Table 2).

Table 2. Comparison of synovial fluid cytokines between groups

	TNF-α	IL-1β	IL-6
Group 1	148.75±22.5	788.46±207.7	83.86±18.0
Group 2	146.41±27.3	735.53±172.6	90.0±16.9
P value	0.806*	0.474*	0.365*

Data are given as median (1st-3rd quartiles), *:Student t test

The correlation between cytokines with preoperative MMO and VAS scores was investigated and there was no statistically significant correlation. A positive correlation was observed between TNF-α and IL-1β, as well as between TNF-α and IL-6. The relationship between TNF-α and IL-1β was positive, strong, and statistically significant (p<0.001, p=0.023). The correlation between IL-6 and IL-1β was not statistically significant (p=0.057) (Chart 1).

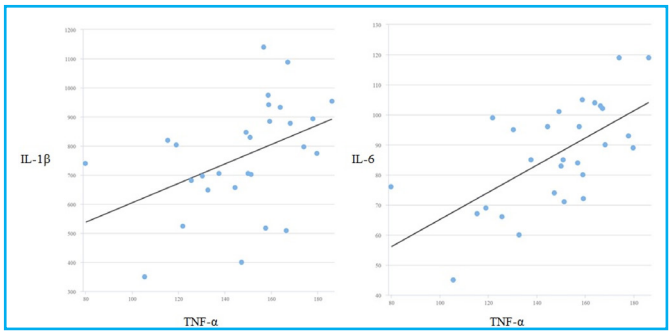

Chart 1. Correlations between IL-1β and IL-6 with TNF-α.

DISCUSSION

The goal of TMJ arthrocentesis is to use hydraulic pressure to wash away inflammatory mediators, release the articular disc, and dissolve adhesions between the disc surface and the articular fossa.[11] Arthrocentesis is a safe and rapid procedure used to treat various disorders affecting TMJ. Arthrocentesis is usually indicated when conservative and pharmacological methods have failed to provide satisfactory results.[6] With arthrocentesis, the intra-articular negative pressure is reduced, and adhesions are eliminated, allowing the disc to be detached from the glenoid fossa ceiling and facilitating condylar translation. Restoring healthy mandibular movements helps eliminate movement restrictions, thereby restoring the mouth opening to normal values.[5] Inflammatory cytokines and pain mediators are removed from the area through arthrocentesis, leading to the treatment of inflammation and alleviation of pain symptoms.[12] In this study, pain scores were measured with a Visual analog scale and it was observed that VAS scores were significantly decreased in all patients after arthrocentesis.

Although there are numerous studies on the pathophysiology of TMJ internal disorders, the exact mechanism of the disease remains not fully understood. In recent years, there are opinions suggesting that changes in the synovial fluid content caused by pro-inflammatory cytokines play a role in the etiology by affecting various molecular mechanisms.[13] In patients with TMJ internal derangement or osteoarthritis, increased hyperemia with capillary vessels and infiltration of inflammatory cells such as T cells or monocytes/macrophages can be visualized in the TMJ synovial membrane through arthroscopic or histopathological analysis.[13]

Cytokines are small proteins released by various cells in response to tissue damage and play a crucial role in cellular signaling. Among cytokines, there are interleukins, tumor necrosis factor, interferons, chemokines, and lymphokines. Some cytokines such as IL-1β, IL-6, IL-8, IL-12, and TNF-α are pro-inflammatory, while others like IL-4 and IL-10 are considered anti-inflammatory.[14]

Many of these cytokines have been found in the synovial fluids of patients with TMJ internal disorders and/or osteoarthritis, and they have been shown to control inflammation processes through various mechanisms. Therefore, these cytokines have been highlighted as promising therapeutic targets for TMJ diseases.[15-17]

Evaluation of the potential roles of cytokines and other mediators has become increasingly important and popular to elucidate the cellular and molecular events in the pathophysiology of TMJ internal disorders and osteoarthritis. In an experimental study conducted by Wang et al.[18] it was shown that in cases where the biomechanical properties of the disc are altered, the expression of IL-1β and TNF-α increased in TMJ, and this condition could impair the adaptive capacity of TMJ. In studies conducted with the biochemical analysis of TMJ synovial fluid, cytokines were investigated by analyzing synovial fluid obtained from patients with TME disorders and comparing it with the MRG (magnetic resonance imaging) images taken from the same patients.[19,20] It was shown that the levels of pro-inflammatory cytokines in synovial fluid were associated with the degree of joint effusion observed in the MRG images.[20] Similarly, it has been reported that the level of IL-6 in synovial fluid is associated with the severity of arthroscopic synovial inflammation.[21] These several investigations have shown that cytokines are involved in the inflammation of the synovium in TMJ. Therefore, in our investigation, based on the literature findings, it was deemed appropriate to use TNF-a, IL-1, and IL-6, which have previously been proven to be present in TMJ, to confirm the existence of inflammation in the retrospectively studied joints.

Synovial cytokines were compared in different patient groups in several studies. Ulmner et al.[22] reported that patients with disc displacement without reduction had higher cytokine concentrations including TNF-α and IL- 1β. On the other hand, Gulen et al.[23] investigated the synovial fluid cytokine levels in patients who had disc displacement with reduction and without reduction and it was reported that synovial fluid cytokine concentrations were not statistically significant between groups. In this study, we similarly observed that there were no statistically significant differences between groups. It is thought that the effect of tissue regeneration and remodeling processes in TMJ may lead to a shift in the dominance of pro-inflammatory cytokines in the early stages of the disease, and in later stages, a greater influence of anti-inflammatory cytokines might be observed. However, since anti-inflammatory cytokines were not investigated in our study, a direct comparison between pro-inflammatory and anti-inflammatory cytokines cannot be made.

The degree of inflammation in TMJ is crucial for the development of pain or clinical symptoms.[14] Some studies investigating IL-1β and TNF-α have shown a relationship between the synovial fluid content and the level of TMJ pain in patients with internal derangement and degenerative changes in TMJ.[8,9] It was reported that higher levels of TNF-α in the synovial fluid of patients with TMJ pain.[24] In another study, a correlation between joint effusion and IL-6 was demonstrated, and since joint effusion is associated with TMJ pain, it is suggested that IL-6 may be related to TMJ pain.[21] However, it is known that non-steroidal anti-inflammatory drugs (NSAIDs) reduce the levels of pro-inflammatory cytokines and the synthesis of prostaglandins. In a study, it was shown that COX (cyclooxygenase) inhibitors suppressed inflammatory mediators such as PGE2, IL-6, and IL-1β in TMJ synovial fluid.[25] Therefore, in studies related to cytokines in TMJ synovial fluid, it is recommended to discontinue NSAID use at least 7-14 days before the analysis.[23] In our study, we did not find any significant relation between clinical signs and cytokine concentrations. Since the study is retrospective, the records of the included patients regarding the use of non-steroidal anti-inflammatory drugs (NSAIDs) are not available. It is important to consider this limitation while interpreting the results and drawing conclusions from the study.

CONCLUSION

Arthrocentesis is beneficial for reducing joint pain in patients with TMJ internal derangements. Synovial fluid contains pro-inflammatory mediators which interact with each other's and pro-inflammatory cytokine levels in synovial fluid are not different in TMJs with disc displacement with and without reduction.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 2019, Decision No: 556).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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The effect of occupational therapy on upper extremity function and activities of daily living in hemiplegic patients

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ABSTRACT

Aims: We aimed to investigate the effectiveness of occupational therapy (OT) added to traditional rehabilitation treatments on activities of daily living and upper extremity functions in hemiplegic patients in this study.

Methods: This study was carried out within eighty hemiplegic patients. In the evaluation of the patients before the therapy, age, gender, body mass index (BMI), occupation, education, duration of stroke, stroke etiology, symptomatic side, the presence of systemic diseases and dominant hand data were recorded. The patients were randomized into two groups according to the sealed envelope method. While standard rehabilitation (ST) (50 minutes five days a week for 6 weeks) was applied to the first group, ST (50 minutes five days a week for 6 weeks) and OT (40 minutes three days a week for 6 weeks) were applied to the second group. Functional Independence Scale (FIM), Fugl-Meyer Upper Extremity Assessment of Motor Recovery Scale (FMA) and Action Research Arm Test (ARAT) were evaluated before the treatment and on the 45th day after the end of the treatment.

Results: Our study included 35 male and 45 female patients. There was no significant difference between the two groups in terms of age, gender, symptom duration and stroke etiology. FIM, ARAT and FMA values were found to be increased in both groups compared to pre-treatment (ST; FIM p=0.003, ARAT p=0.011, FMA p= 0.002 OT; FIM p=0.023, ARAT p=0.024, FMA p= 0.012). While there was no significant difference in terms of FIM, ARAT and FMA values before treatment in comparisons between groups, all parameters were found to be significantly increased in the OT group compared to ST on the 45th day of treatment (FIM p=0.017, ARAT p=0.021, FMA p= 0. 004).

Conclusion: In this study, OT was applied three times a week for 40 extremity dexterity. While the increase in FIM, FMA and ARAT was significant after treatment in both groups, the increase in the OT group was higher when compared to ST. The results of our study show that both ST and OT are effective in stroke rehabilitation. In addition, it has been clearly proven that more effective results are obtained in upper extremity functions with OT added to ST.

Keywords: Hemiplegia, occupational therapy, upper limb

INTRODUCTION

Stroke is a clinical syndrome with symptoms lasting 24 hours or longer, with no obvious cause other than vascular origin and often with focal deterioration in cerebral functions.[1] Stroke is a serious neurological disease and over the last two decades there has been an increase in deaths from stroke by 43%.[2,3] Despite the advances in stroke prevention and treatment, it is an important health problem that affects a large part of the society with its high incidence and mortality and causes disability in survivors. Post-stroke disability reduces the patient's quality of life, affects the lives of patients' relatives and causes both socioeconomic and social problems.[4] Only 10% of post-stroke patients show complete recovery and 60% suffer from chronic dysfunction.[5] Upper limb function after stroke is the main cause of long-term disability so rehabilitation research is a top priority. Although nerve reorganization occurs soon after stroke, the natural rehabilitation of upper limb function recovery is usually limited.[6] Upper limb paresis is observed in 87% of stroke survivors.[7] Furthermore, impaired use of the upper limb persists in about 60% of the patients 6 months post-stroke.[8] Early exercise interventions are necessary to improve upper extremity motor functions and activities of daily living (ADL), as persistent upper extremity dysfunction is strongly associated with decreased activities of daily living and poor quality of life after stroke.[9-11]

Occupational therapy (OT) is a part of medical rehabilitation therapy aimed at restoring, strengthening and increasing the person's performance in specified activities and tasks in order to improve health, reduce and correct pathology.[4] Studies have shown that OT shortens the length of hospital stay, increases activities

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of daily living, and increases the level of independence in stroke patients.[12,13] Although the incidence of ischemic and hemorrhagic strokes is high worldwide annually, the optimal dose and timing for OT are entirely unclear.

Stroke remains one of the leading causes of death and disability in world, and projections show that the burden of stroke will not decrease in the next decade or beyond.[14] After a stroke, one of the main sequelae produced is the loss of mobility in the upper extremities of the human body. Therefore, in the assessment of upper extremity function it's important to improve the effectiveness of rehabilitation programs, and the use of standardized outcome measures which can lead to more efficient rehabilitation programs for post-stroke patients.[15] Therefore, we aimed to investigate the effectiveness of OT added to traditional rehabilitation treatments on activities of daily living and upper extremity functions in hemiplegic patients in this study.

METHODS

Sixty patients with hemiplegia who applied to Erol Olçok Training and Research Hospital Physical Medicine and Rehabilitation Clinic were included in the study. The study was approved by the Hitit University Clinical Researches Ethics Committee (Date: 24.05.2023, Decision No: 2023-67). A well-informed written consent was obtained from all participants according to the principles of the Declaration of Helsinki. The inclusion criteria were 18-75 years of age, diagnosed with stroke for the first time, not more than 12 months after stroke and no cognitive dysfunction. Exclusion criteria were aphasic patients, the presence of flaccid hemiplegia, the presence of spasticity above grade 3 in the upper extremity according to the Modified Ashworth Scale (MAS) and the absence of sitting balance. In the evaluation of the patients before the therapy, age, gender, body mass index (BMI), occupation, education, duration of stroke, symptomatic side, the presence of systemic diseases and dominant hand data were recorded. All patients underwent detailed neuromuscular system examination before treatment and at controls. The patients were randomized into two groups according to the sealed envelope method. While standard rehabilitation (ST) (50 minutes five days a week) was applied to the first group, ST (50 minutes five days a week) and OT (40 minutes three days a week) were applied to the second group. Conventional rehabilitation exercises such as passive, active and active-assisted range of motion, strengthening, balance coordination exercises, transfer training exercises, walking and climbing stairs were applied to the patients in the ST group, accompanied by a physiotherapist. A trained occupational therapist performed OT. The treatment balls, colored cylinders, perforated circles, wooden blocks, skill house and skill cubes were used during the treatment.

Parametres

All parameters were evaluated before the treatment and on the 45th day after the end of the treatment.

Functional independence measures (FIM) : The FIM includes measures of independence for self-care. It is an 18-item, seven-level, ordinal scale. The total score (sum of motor and cognition subscale scores) for the FIM tool will be a value between 18 and 126.[16]

Fugl-Meyer upper extremity assessment of motor recovery scale (FMA): It is a subsection of the Fugl Meyer Rating Scale. This scale, which includes 33 items, evaluates the movement, coordination and reflexes of the shoulder, elbow, forearm, wrist and fingers. In the scale with a maximum score of 66, it is scored as "0: movement cannot be performed", "1: movement is partially performed" and "2: movement is performed normally", except for items including reflex activity and coordination and speed assessment.[17]

Action research arm test: It is a responsive and valid measure of upper limb functional limitation and is a useful measure for use in upper limb rehabilitation and clinical research. It has 4 subgroups measuring gross, fine, and fingertip grip and coarse motion and 19 evaluation items. The upper extremity motor function assessment was done in the current study by scoring each item in the following order as 0: cannot do movement, 1: does (completes) movement partially, 2: does the movement with difficulty in an abnormally long time, and 3: does the movement normally (with no difficulty).[18]

Statistical Analysis

Analyzes were made with the SPSS 23.0 program. Descriptive statistics are presented with frequency, percentage, mean, standard deviation, median, minimum and maximum values. Non-parametric data were analyzed using the Wilcoxon signed ranks test to investigate within-group differences; a paired sample t-test was applied to compare intragroup changes of normally distributed variables. Independent t-tests were performed to compare the means between the groups for normally distributed data, while MannWhitney U test was utilized for non-parametric variables without normal distribution. The nominal variables were examined by the Pearson Chi-square test or Fisher's Exact test. The results were assessed within 95% reliance and at a significance level of $p<0.05$.

RESULTS

Our study included 35 (43.75%) male and 45 (56.25%) female patients. The mean age of the patients was 67.03±8.96 years. There were 40 patients in both groups and the majority of patients were women. There was no

significant difference between the two groups in terms of age, gender, symptom duration and stroke etiology (Table 1). FIM, ARAT and FMA values were found to be increased in both groups compared to pre-treatment (ST; FIM p=0.003, ARAT p=0.011, FMA p= 0.002 OT; FIM p=0.023, ARAT p=0.024, FMA p= 0.012) (Table 2). While there was no significant difference in terms of FIM, ARAT and FMA values before treatment in comparisons between groups, all parameters were found to be significantly increased in the OT group compared to ST on the 45th day of treatment (FIM p=0.017, ARAT p=0.021, FMA p= 0. 004) (Table 3).

Table 1. Demographic and clinical characteristics of the treatment groups

	ST group (n=40)	OT group (n=40)	p value
Age (Mean±SD)	67,8 ± 4,9	66,8 ± 4,2	0.088
Gender (F/M)	23/17	22/18	0.613
Dominant extremity (right/left)	34/6	36/4	0.173
Symptom Duration (month)	9.12±1.23	9.45±1.45	0.256
Stroke etiology Ischemic/haemorrhagic	32/8	34/6	0.453

ST: Standard treatment, OT: Occupational therapy, F/M: Female/Male, SD: Standart Deviation

Table 2. Comparison of ARAT, FIM and FMA on values of ST and OT groups in two stages

	Before treatment Mean±SD	45th day after treatment Mean±SD	p value
ST group			
FIM	72.11± 14.3	83.16± 15.8	0.003
ARAT	48.73±11.6	52.31±11.4	0.011
FMA	53.21±12.8	58.72±12.5	0.002
OT group			
FIM	73.18±16.9	90.3±15.7	0.023
ARAT	48.36±10.4	54.71±11.03	0.024
FMA	51.4±13.01	61.73±13.5	0.012

ST: Standard treatment, OT: Occupational therapy FIM: Functional Independence Scale, FMA:Fugl-Meyer Upper Extremity Assessment of Motor Recovery Scale, ARAT: Action Research Arm Test

Table 3. Comparison of ARAT, FIM and FMA scores of the patients before the treatment, and at the 45th day of the treatment between groups

		ST Mean±SD	OT Mean±SD	p value
FIM	Before treatment	72.11± 14.3	73.18±16.9	0.162
	45th day of treatment	83.16± 15.8	90.3±15.7	0.017
ARAT	Before treatment	48.73±11.6	48.36±10.4	0.075
	45th day of treatment	52.31±11.4	54.71±11.03	0.021
FMA	Before treatment	53.21±12.8	51.4±13.01	0.237
	45th day of treatment	58.72±12.5	61.73±13.5	0.004

SD: Standart Deviation, ST: Standard treatment, OT: Occupational therapy FIM: Functional Independence Scale, FMA:Fugl-Meyer Upper Extremity Assessment of Motor Recovery Scale, ARAT: Action Research Arm Test

DISCUSSION

The results of our study show that OT added to traditional rehabilitation treatments improves the upper extremity functions and increases independence levels in hemiplegic patients. Although ARAT, FIM and FMA values were found to be increased in the groups receiving ST and OT treatment added to ST, compared to pretreatment, this increase was found to be more significant in the OT group compared to the ST group. Ageing is regarded as the most important predictor of stroke incidence and mortality, and thus, their rates increase by age. 88% of global strokes occur above age 65 years.[19] The mean age of the patients was 67.03±8.96 years ın our study. Ischemic stroke is the most common type of stroke, accounting for about 80% stroke.[20] The majority of the patients in our study had a history of ischemic stroke. In an epidemiological study conducted in our country, it was reported that 54.3% of strokes were seen in women.[21] Similar to the literature, female patients were more common than males in our study. Motor and sensory disorders in the upper extremity limit the daily life activities of the person and increase the rate of dependence on others more than the disability in the lower extremities. In stroke rehabilitation, rehabilitation of the upper extremity is important in order to gain independence in daily living activities.[22] Although studies have been reported showing that OT has positive results in the acquisition of new motor skills in the upper extremity, there is no consensus in the literature on the duration of OT application. In the study of Aydilek et al.[4] on 48 patients with hemiplegia, two treatment groups were compared. The patients in the first group were treated with standard rehabilitation (5 days for 6 weeks, 45 minutes a day) plus OT (5 days for 6 weeks, 45 minutes a day), while the patients in the second group were applied only standard rehabilitation. In the results of the 6th week after the treatment; It was observed that there was a statistically significant increase in the Barthel Index (BI), FMA Scale and ARAT scores of the patients in both the ST and OT groups compared to pre-treatment. While there was a statistically significant difference in the comparison of the FMA Scale and ARAT scores between the groups after treatment, there was no significant difference between the groups in the BI scores. In a prospective randomized controlled study carried out by Rabadi et al.[23] with 30 acute stroke patients, the study patients were divided into 3 groups. The 1st group received ergotherapy training, 2nd group nonresistant continuous arm ergometry, and 3rd group robot-assisted therapy. In addition, standard rehabilitation treatment was applied to all groups. The study results yielded no statistically significant difference in the Functional Independence Measure (FIM) scale, FMA scale, ARAT, and MAS scores. Ultimately, robotic rehabilitation and arm ergometry appeared not to show

superiority to OT in improving upper extremity motor functions in acute stroke patients. In a randomized controlled study by Alsubiheen et al.[6] aimed to investigate the effects of 6 week in two 1.5 hours sessions/week task-oriented activities of daily living training on upper limb functions, activities of daily living (ADL), and quality of life (QoL) in chronic stroke patients. It has been shown that eight-week training has a positive effect on upper extremity functions and coarse dexterity and OT is effective in improving ADL and QoL in chronic stroke patients. In a randomized study by Almhdawi et al.[24] in which they evaluated the functional and impairment effects of the OT approach on the upper extremity after stroke, they showed that 3 hours/week for 6 weeks provided clinically significant functional improvements. In a study of 138 hemiplegic patients, Gilbertson et al.[25] compared OT with ST. BI was found to be significantly higher in the OT group at 6 months. Narayan et al.[26] evaluated 103 stroke patients by separating them into two groups. The first group received one hour of OT for meaningful tasks for four weeks, and the second group standard rehabilitation therapy during the same period. The patients were assessed with ARAT, FMA Scale, Wolf Motor Function Test, and Motor Activity Diary-28 at initial, at the 4th and 8th weeks of the treatment. Finally, it was revealed that OT provided statistically and clinically significant improvements in stroke patients' upper extremity motor recovery. In a study of Ayna et al.[27] patients with hemiplegia were assigned into two groups, conventional therapy (five days in a week, for four weeks) and occupational therapy in the content of repetitive task specific training (an hour once in a day, five days in a week, for four weeks) were performed for group 1, only conventional therapy was performed for group 2. There was not a significant statistical difference between two group's outcome parameters. While there was statistically significant improvements for upper extremity Brunstromm grade and emotional reactions subtitle of Nottingham Health Profile (NHP) in group 1, there were no significant improvements in group 2. In our study, OT was applied three times a week for 40 extremity dexterity. While the increase in FIM, FMA and ARAT was significant after treatment in both groups, the increase in the OT group was higher when compared to ST. The results of our study show that both ST and OT are effective in stroke rehabilitation. In addition, it has been clearly proven that more effective results are obtained in upper extremity functions with OT added to ST.

Limitations

Our study has some limitations. Most importantly, we did not classify stroke patients as acute, subacute and chronic stroke. Other limitations are that the small number of subjects, long-term efficacy was not evaluated and it was a single-center study. The efficacy of both ST and OT may not be standardized and may not be well documented depending on the patient-oriented natures of the rehabilitative programs.

CONCLUSION

OT is a part of medical rehabilitation therapy aimed at restoring, strengthening and increasing the person's performance in specified activities and tasks in order to improve health, reduce and correct pathology. OT shortens the length of hospital stay, increases activities of daily living, and increases the level of independence in stroke patients. The optimal dose, timing and treatment protocol for OT are entirely unclear. In this regard, we believe that we will contribute to the literature with our results regarding the duration of OT treatment in stroke patients. Multicenter studies with a larger number of patients will be more useful in determining the appropriate protocol of OT.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Clinical Researches Ethics Committee (Date: 24.05.2023, Decision No: 2023-67).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The role of the TAPSE/PASP ratio in the prediction of paroxysmal atrial fibrillation in patients with acute ischemic stroke

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ABSTRACT

Aims: Atrial fibrillation (AF) remains the most prevalent cause of cardioembolic stroke. Paroxysmal AF (PAF) is often difficult to be diagnosed and is sometimes first detected during embolic stroke. Yet, TAPSE and PASP can be easily revealed in routine transthoracic echocardiography (TTE). Then, the TAPSE/PASP ratio is often shown to have prognostic significance in many cardiac disorders. Nevertheless, the insufficient scholarly knowledge of the relationship between this ratio and the development of PAF became the primary motive of the present study.

Methods: We carried out this study with 114 patients experiencing acute ischemic stroke without a previous diagnosis of AF. We noted down the patients' blood parameters and prescribed drugs and calculated TAPSE/PASP ratio relying on their TTE findings. We also recorded the 24-hour heart rhythm findings of each patient through Holter monitoring. After categorizing PAF attacks (i.e.,PAF attack was (not) observed), we explored any statistical relationship between the TAPSE/PASP ratio and the presence of PAF.

Results: The findings revealed a significant difference between the TAPSE/PASP ratios between the groups with PAF (0.62±0.07) and without PAF (0.77±0.08). Moreover, the receiver operating characteristic (ROC) curve analysis yielded the TAPSE/PASP ratio to demonstrate a diagnostic value in predicting PAF (area under the ROC curve [AUC]=0.89;82.7%; p<0.001). Besides, the TAPSE/PASP ratio measured <0.67 at admission was found to have 87.1% sensitivity and 82.7% specificity in predicting PAF. Finally, the multivariate analysis showed the TAPSE/PASP ratio to be a significant risk factor for PAF (odds ratio [OR]=2.971;95% confidence interval [CI]=1.073-8.959; p=0.000).

Conclusion: Overall, a low TAPSE/PASP ratio (<0.67) may be a precursor of the presence of PAF in patients.

Keywords: Acute ischemic stroke, tricuspid annular plane systolic excursion, mean pulmonary artery systolic pressure, paroxysmal atrial fibrillation

INTRODUCTION

Stroke remains to be a major cause of neurological morbidity and mortality worldwide.[1] While it is known that cardiac embolism accounts for about 20% of all ischemic strokes,[2-4] atrial fibrillation (AF) continues to be the most prevalent cause of cardioembolic stroke.[3-5] Acute myocardial infarction (AMI), ventricular thrombus, structural heart defects, heart tumors, and heart valve disease can be shown as other causes of cardioembolic stroke.[4] According to the American College of Cardiology, the American Heart Association, and the European Society of Cardiology, AF is classified in different forms:6 1) Paroxysmal AF (PAF), a self-terminating or intermittent form, usually takes less than seven days and less than 24 hours; 2) Persistent AF is not self-limiting and lasts longer than seven days; 3) permanent AF lasts more than a year. PAF can also be particularly difficult to detect and is sometimes first detected during an embolic stroke.

Yet, tricuspid annular plane systolic excursion (TAPSE) and mean pulmonary artery systolic pressure (PASP) can be quickly revealed in routine transthoracic echocardiography (TTE). Then, the TAPSE/PASP ratio is often shown to have prognostic significance in many cardiac disorders. Despite being the subject of research on cardiac disorders, the TAPSE/PASP ratio has not appeared with the development of PAF so far. Therefore, the present study was intended to explore the role of the TAPSE/PASP ratio in predicting PAF.

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METHODS

The study was carried out with the permission of theBalıkesir University Clinical Researches Ethics Committee (Date: 05.17.2023, Decision No: 2023-55). In all stages of the study, we strictly adhered to the rules and the principles set forth in the Declaration of Helsinki.

Our study was designed retrospectively. The subjects were enrolled randomly files. We carried out this single-center study with 114 patients hospitalized in the neurology department due to the diagnosis of acute ischemic stroke and for whom we consulted the cardiology clinic for cardioembolic etiology. Despite no age-related criterion, we set the exclusion criteria as follows: the presence of permanent or persistent AF, chronic obstructive pulmonary disease (COPD), severe heart valve disease, moderate to severe renal failure (Glomerular Filtration Rate (GFR) below 60 mL/min), severe anemia, antiarrhythmic drug use, congenital heart disease, mild to advanced pulmonary hypertension, history of malignancy, hepatic dysfunction (the presence of cirrhosis or alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] > 3×Upper limit of the normal range (ULN) and total bilirubin > 2×ULN), alcohol/substance abuse, and active infection. TTE was performed using the Esaote My Lab seven (Getz Healthc are Malaysia) device in the left lateral position. While the TAPSE value was noted down in millimeters by aligning the lateral part of the cursor tricuspid valve with M-mode echocardiography, measuring the peak from the end of diastole to the end of systole (averaging 3 to 5 beats), the PASP value was obtained from the tricuspid regurgitation (TR) jet velocity using the simplified Bernoulli equation. Then, the TAPSE/PASP ratio was calculated by dividing the TAPSE value by the mean pulmonary artery pressure value. Two experienced cardiologists who were blinded to the study protocol took all measurements.

The definition of the AF7;

- Absence of P waves,
- Irregular R-R interval,

The above two criteria are defined as AF if present either ≥ 30 seconds on the 24-hour rhythm holter or on the entire 12-lead standard electrocardiogram.

If the AF rhythm terminates spontaneously, it is defined as PAF.6 We decided on PAF according to the presence or absence of the AF criteria mentioned above in the 24-hour Holter monitoring and divided the patients into 2 groups according to the presence or absence of AF. (i.e., PAF attack was not observed [without PAF], and PAF attack was observed [with PAF]). In our study, at least 1 AF attack that lasted ≥ 30 seconds and ended spontaneously in 24-hour Holter monitoring was considered as PAF. Total duration and number of AF was not calculated in 24-hour Holter monitoring. Patients with at least 1 AF rhythm for ≥ 30 seconds in 24-hour Holter monitoring were included in the PAF group. Patients with AF rhythm of < 30 seconds and/or patients without AF rhythm in 24-hour Holter monitoring were included in the group without PAF.

While we defined hypertension (HT) as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and any antihypertensive use as drug therapy8,diabetes mellitus (DM) was defined as fasting blood glucose level ≥126 mg/dL, blood glucose level ≥ 200 mg/dL two hours after oral glucose tolerance test, HbA1c value > 6.5, or random blood glucose ≥ 200 mg/dL9. We also recorded the drugs prescribed to the patients for these disorders (antidiabetics, antihypertensives, antiaggregants, and antihyperlipidemics). Finally, while considering complete blood count parameters to be white blood cell (WBC) count, hemoglobin (Hb), hematocrit (HCT), platelet (PLT), mean platelet volume (MPV), red cell distribution width (RDW), and mean cell volume (MCV), we accepted biochemistry parameters as blood glucose, urea, and creatinine levels at admission.

Statistical Analysis

First off, we resorted to the Kolmogorov-Smirnov test to explore the data distribution. Accordingly, while normally-distributed continuous variables are expressed as means (M) ± standard deviations (SD), we present non-normally distributed continuous variables as medians (interquartile range). Then, we ran the pairwise comparison using independent samples t-test or Mann-Whitney U-test. On the other hand, the categorical variables -demonstrated as absolute and relative frequencies - were compared using the chi-square test. Besides, we performed the receiver operating characteristics (ROC) curve analysis to set the sensitivity, specificity, and cut-off value of the TAPSE/PASP ratio in predicting PAF. Moreover, the variables with a p-value <0.25 in the univariate analysis were considered potential risk factors for PAF attacks and were included in the full model in the multivariate logistic regression analysis. Finally, we performed all statistical analyses on SPSS 22.0 for Windows (Armonk, NY: IBM Corp.) and considered a p-value < 0.05 to be statistically significant.

RESULTS

The mean age of the patients, 58 (50.9%) males and 56 (49.1%) females, was found to be 69.1±11.0 years. We detected DM in 36.8% of the patients, HT in 63.2%, and coronary artery disease (CAD) in 26.3%. The patients' mean body mass index (BMI) was 27.5, and 28.1% were diagnosed with COVID-19. Echocardiographic (echo) findings showed the mean size of the left atrial (LA) to be 37.1±3.9 mm. Besides, ejection fraction was found

to be above 50 % in 86 % of the patients, between 40-50% in 8.8%, and below 4 % in 5.3 BMI%. AF rhythm of ≥ 30 seconds was detected in 45.6% of the patients, while 54.4% had no AF rhythm or, if any, it was less than 30 seconds. No abnormal values were observed in their biochemical parameters (Table 1).

Table 1. Key clinical characteristics of the sample (n=114)

Clinical characteristics	
Age (years)	69.1± 11.0
Sex (male), n (%)	58 (50.9)
Diabetes, n (%)	42 (36.8)
Hypertension, n (%)	72 (63.2)
Coronary artery disease, n (%)	30 (26.3)
Smoking, n (%)	34 (29.8)
BMI, n (%)	27.5 (25.8-30.6)
COVID-19, n (%)	32 (28.1)
Cardiac characteristics	
LA diameter, mm	37.1± 3.9
PAF, n (%)	
Absence of AF rhythm	62 (54.4)
≥30 seconds AF rhythm	52 (45,2)
EF, n (%)	
≥%50	98 (86.0)
%40-%50	10 (8.8)
<%40	6 (5.3)
Heart rate (per minute)	73.8± 11.6
Biochemical parameters	
HB, g/dL	12.8± 1.8
HCT, %	38.0± 6.9
PLT, mm3	245.1± 83.4
MPV, fL	10.1 (9.5-11.1)
RDW	14.0 (13.3-14.8)
Urea, mg/dL	38.4± 18.1
Creatinine, mg/dL	0.85 (0.72-1.07)
Drug use	
ACE-ARB, n (%)	46 (40.4)
Beta blocker, n (%)	36 (31.6)
OAD-Insulin, n (%)	40 (35.1)
Clopidogrel, n (%)	22 (19.3)
Statin, n (%)	24 (21.1)
CCB, n (%)	38 (33.3)
ASA n (%)	42 (36.8)
Diuretics, n (%)	28 (24.6)
TAPSE/PASP ratio	0.70 ± 0.10

Normally-distributed continuous variables are expressed as means (M)±standard deviations (SD). Non-normally distributed data are presented as medians (interquartile range). Categorical variables are demonstrated as numbers (n) and percentages (%). BMI: body mass index; LA: left atrium; AF: atrial fibrillation; PAF: paroxysmal atrial fibrillation; EF: ejection fraction; HB: hemoglobin; HCT: hematocrit; PLT: platelet count; MPV: mean platelet volume, RDW: erythrocyte distribution width; TAPSE/PASP: the tricuspid annular plane systolic excursion/mean pulmonary artery systolic pressure ratio; ACE :Angiotensin-converting enzyme; ARB: Angiotensin-2 receptor blockers.

Table 2 presents the analysis findings between patients with and without PAF attacks. Accordingly, the mean age of the patients with PAF attacks was found to be significantly higher. Although we could not detect significant differences between the groups by sex, DM, CAD, BMI, and COVID-19 history, HT was significantly more prevalent in the group with PAF attacks. Conversely, the PAF-free group hosted more patients persisting in smoking. When it comes to the echo parameters, the LA size was significantly larger in the group with PAF. Except for hemoglobin and hematocrit values (significantly higher in the PAF-free group), the groups did not significantly differ by other biochemical parameters; it was also the case regarding drug use. Nevertheless, there was a significant difference between the groups by TAPSE/PASP ratio; the PAF group had a significantly lower TAPSE/PASP (0.62±0.07 vs. 0.77±0.08; p< 0.01)

Table 2. Comparison of the PAF groups

	PAF (-)	PAF(+)	p
Clinical characteristics			
Age (years)	65.7± 12.2	73.1± 7.7	0.00
Sex (male), n (%)	32 (51.6)	26 (%50.0)	0.86
Diabetes, n (%)	20 (32.3)	22 (42.3)	0.26
Hypertension, n (%)	32 (51.6)	40 (76.9)	0.00
Coronary artery disease, n (%)	16 (25.8)	14 (26.9)	0.89
Smoking, n (%)	26 (41.9)	8 (15.4)	0.00
BMI, n (%)	27.3 (25.9-30.4)	27.9 (24.2-31.5)	0.84
COVID-19, n (%)	14 (22.6)	18 (34.6)	0.15
Cardiac characteristics			
LA diameter, mm	35.3± 2.7	39.4± 4.0	0.00
EF, n (%)			0.35
≥%50	56 (90.3)	42 (80.8)	
%40-%50	4 (6.5)	6 (11.5)	
<%40	2 (3.2)	4 (7.7)	
Heart rate	72.8± 11.7	74.9± 11.6	0.35
Biochemical parameters			
HB, g/dL	13.4± 1.7	12.0± 1.6	0.00
HCT, %	40.0± 5.1	36.7± 4.6	0.00
PLT, mm3	251.4± 92.1	237.6± 71.9	0.38
MPV, fL	10.0 (9.5-11.4)	10.1 (9.6-11.1)	0.13
RDW	13.8 (12.9-14.5)	14.2 (13.6-15.1)	0.06
Urea, mg/dL	37.7± 16.9	39.4± 19.6	0.61
Creatinine, mg/dL	0.82 (0.73-1.04)	0.93 (0.70-1.16)	0.11
Drug use			
ACE-ARB, n (%)	20 (32.3)	26 (50.0)	0.06
Beta blocker, n (%)	20 (32.3)	16 (30.8)	0.86
OAD-Insulin, n (%)	20 (32.3)	20 (38.5)	0.48
Clopidogrel, n (%)	12 (19.4)	10 (19.2)	0.98
Statin, n (%)	14 (22.6)	10 (19.2)	0.66
CCB, n (%)	14 (22.6)	24 (46.2)	0.00
ASA n (%)	24 (38.7)	18 (34.6)	0.65
Diuretics, n (%)	14 (22.6)	14 (26.9)	0.59
TAPSE/PASP ratio	0.77 ± 0.08	0.62 ± 0.07	0.00

Normally-distributed continuous variables are expressed as means (M)±standard deviations (SD). Non-normally distributed data are presented as medians (interquartile range). Categorical variables are demonstrated as numbers (n) and percentages (%). BMI: body mass index; LA: left atrium; PAF: paroxysmal atrial fibrillation; EF: ejection fraction; HB: hemoglobin; HCT: hematocrit; PLT: platelet count; MPV: mean platelet volume, RDW: erythrocyte distribution width; TAPSE/PASP: the tricuspid annular plane systolic excursion/mean pulmonary artery systolic pressure ratio

The ROC analysis verified the diagnostic value of the TAPSE/PASP ratio in predicting PAF (area under the ROC curve [AUC]=0.89; 82.7%; p< 0.001). Besides, the TAPSE/PASP ratio measured below 0.67 at admission was found to have 87.1% sensitivity and 82.7% specificity in predicting PAF (Figure 1).

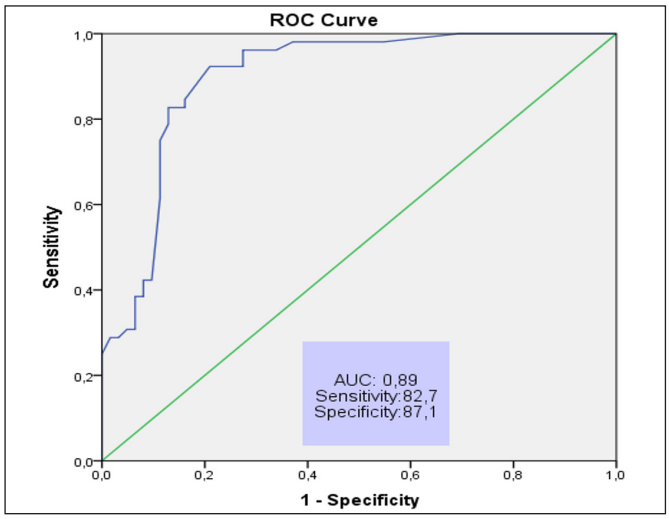

Figure 1. ROC curve of the TAPSE/PASP ratio in predicting PAF (ROC: receiver operating characteristic)

The box-plot plot in Figure 2 also showed that the PAF group had a significantly lower TAPSE/PASP ratio. On the other hand, the error terms were divided into two by the cut-off value of the TAPSE/PASP ratio (0.67), and our findings did not reveal a significant difference between the groups by gender, DM, CAD, BMI, and COVID-19 history. Nonetheless, the group with a TAPSE/PASP ratio <0.67 had a significantly higher mean age, more HT, and less smoking. Besides, the patients with a TAPSE/PASP ratio <0.67 had a significantly higher LA size. Except for hemoglobin and hematocrit values, biochemical parameters were found to be significantly lower in the group with a TAPSE/PASP ratio < 0.67. The groups did not significantly differ by drug use; only the Angiotensin-converting enzyme-Angiotensin-2 receptor blockers (ACE-ARB) ratio was significantly higher in the group with TAPSE/PASP ratio < 0.67 (Table 3).

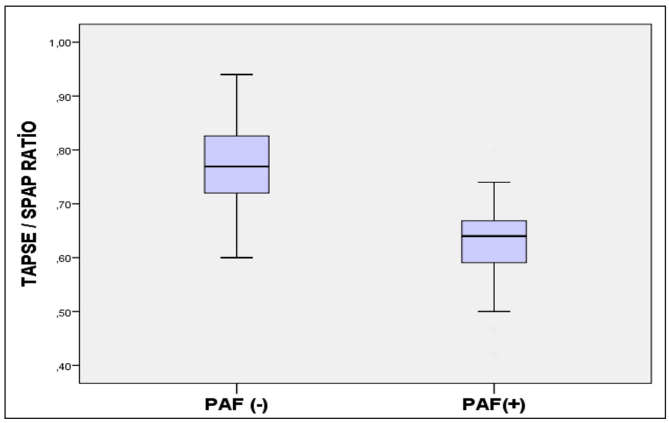

Figure 2. Box-plot of the TAPSE/PASP ratio in the patient groups with and without PAF attacks

Table 3. Clinical characteristics of the sample by the TAPSE/PASP ratio

	TAPSE/PASP <0.67	TAPSE/PASP ≥0.67	p
Clinical characteristics			
Age (years)	72.2± 8.2	66.5± 12.3	0.00
Sex (male),n (%)	28 (54.9)	30 (47.6)	0.43
Diabetes, n (%)	23 (45.1)	19 (30.2)	0.10
Hypertension, n (%)	41 (80.4)	31 (49.2)	0.00
Coronary artery disease, n (%)	15 (29.4)	15 (23.8)	0.49
Smoking, n (%)	8 (15.7)	26 (41.3)	0.00
BMI, n (%)	27.6 (25.3-31.2)	27.3 (25.9-30.4)	0.46
COVID-19, n (%)	16 (31.4)	16 (25.4)	0.48
Cardiac characteristics			
LA diameter, mm	38.8± 4.2	35.8± 3.1	0.00
EF, n (%)			0.32
≥%50	41 (80.4)	57 (90.5)	
%40-%50	6 (11.8)	4 (6.3)	
<%40	4 (7.8)	2 (3.2)	
Heart rate	74.2± 12.5	73.4± 11.0	0.69
Biochemical parameters			
HB, g/dL	12.3± 1.7	13.2± 1.8	0.00
HCT, %	37.4± 4.8	39.4± 5.3	0.03
PLT, mm3	243.4± 67.6	246.5± 94.8	0.84
MPV, fL	10.0 (9.6-11.1)	10.3 (9.5-11.2)	0.69
RDW	14.3 (13.6-15.1)	13.8 (12.9-14.5)	0.11
Urea, mg/dL	39.2± 19.3	37.9± 17.2	0.70
Creatinine, mg/dL	0.91 (0.70-1.16)	0.82 (0.73-1.04)	0.53
Drug use			
ACE-ARB, n (%)	27 (52.9)	19 (30.2)	0.01
Beta blocker, n (%)	18 (35.3)	18 (28.6)	0.44
OAD-Insulin, n (%)	21 (41.2)	19 (30.2)	0.22
Clopidogrel, n (%)	11 (21.6)	11 (17.5)	0.58
Statin, n (%)	11 (21.6)	13 (20.6)	0.90
CCB, n (%)	25 (49.0)	13 (20.6)	0.00
ASA n (%)	20 (39.2)	22 (34.9)	0.63
Diuretics, n (%)	14 (27.5)	14 (22.2)	0.51

Normally-distributed continuous variables are expressed as means (M)±standard deviations (SD). Non-normally distributed data are presented as medians (interquartile range). Categorical variables are demonstrated as numbers (n) and percentages (%). BMI: body mass index; LA: left atrium; PAF: paroxysmal atrial fibrillation; EF: ejection fraction; HB: hemoglobin; HCT: hematocrit; PLT: platelet count; MPV: mean platelet volume, RDW: erythrocyte distribution width; TAPSE/PASP: the tricuspid annular plane systolic excursion/mean pulmonary artery systolic pressure ratio

We subjected the risk factors that may affect the presence of PAF and the TAPSE/PASP ratio to univariate and multivariate logistic regression analyses. In univariate analysis, the variables with a p-value <0.25 were identified as potential risk factors for PAF and included in the entire model. Then, the multivariate analysis yielded that the TAPSE/PASP ratio was found to be a significant risk factor for PAF (odds ratio [OR]= 2.971; 95% confidence interval [CI]=1.073-8.959; p=0.000) (Table 4).

Table 4. Results of the univariate and multivariate logistic regression analyses

	Unadjusted OR	95% CI	p	Adjusted OR	95% CI	p
Age	1.074	1.031-1.119	0.001	1.070	1.011-1.133	0.019
Sex	1.067	0.510-2.230	0.864			
Diabetes	1.540	0.716-3.312	0.269			
Hypertension	3.125	1.383-7.060	0.006	1.110	0.346-3.560	0.860
Coroner artery disease	1.059	0.459-2.444	0.893			
BMI	1.005	0.948-1.066	0.865			
TAPSE/PASP	3.225	1.147-9.062	0.000	2.971	1.073-8.959	0.000

BMI: body mass index; CI: Confidence interval; OR: odds ratio. TAPSE/PASP: the tricuspid annular plane systolic excursion/mean pulmonary artery systolic pressure ratio

DISCUSSION

Relying on our findings, we concluded that the TAPSE/PASP ratio is more likely to guide one to detect PAF, a leading etiological cause of acute ischemic stroke. It should be noted that PAF was highly suspected in the patients with a TAPSE/PASP ratio of < 0.67, even if PAF could not be detected in their 24-hour Holter monitoring. Thus, it is highly recommended to check longer-term or recurrent rhythm Holter monitoring among such patients.

In their hallmark Framingham study in 1978, Wolf et al.[10] established the relationship between non-valvular AF and stroke by documenting that patients with AF have a 5-fold higher risk of ischemic stroke compared to those without AF. Moreover, the ACTIVE W trial (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) showed the rate of stroke/systemic embolization to be 2.0% in patients with PAF and 2.2% in those with permanent AF.[11] Similarly, SPAF research demonstrated the annual rate of ischemic stroke to be 3.2% among those with PAF and 3.3% in patients with permanent AF.[12] Besides, the ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) study reported a linear relationship between PAF and stroke risk.[13] However, growing evidence suggests a robust association between the burden of AF and the risk of subsequent ischemic events. In this sense, the detection of PAF may be critical to the emergence of recurrence of acute ischemic stroke. Thus, we carried out this study hinging upon the idea that it would be helpful to explore other predictors other than Holter monitoring to detect PAF.

The literature hosts a plethora of research adopting different echo parameters and biomarkers to predict PAF. For example, XU et al.[14] reported that LA reservoir function, impaired diastolic emptying index, and an elevated BNP level may serve as valuable predictors of PAF relapse in patients undergoing catheter ablation. In this study, we may present several reasons for choosing the TAPSE/PASP ratio as the predictor of PAF. 1) In their study, Guazzi et al.[15] found the TAPSE/PASP ratio (< 0.35) to be significantly lower in patients with AF. Similar to our study, many other studies on heart failure with preserved ejection fraction (HFpEF) reported AF to be prevalent,[16,17] and associated with the severity of right heart disease. AF and heart failure often emerge together, resulting in increased morbidity and mortality compared to either disorder. One also needs to acknowledge that AF and heart failure share common mechanisms and treatment strategies.[18] 2) In addition, Guazzi et al.[15] observed that the left atrium (LA) size was significantly larger (40.6±16.7 ml/m²) in those with a low TAPSE/PASP ratio (<0.35).15 Benjamin et al.[19] documented that every 10 mm increase in LA size among men and women enrolled in the Framingham Heart Study led to ~40% and >100% increases in stroke, respectively. In addition, LA size was previously reported to predict ischemic stroke recurrence in patients with nonvalvular AF.[20,21] The close link between LA size and AF and the inverse correlation between the TAPSE/PASP ratio and LA size inspired our research question of whether the TAPSE/PASP ratio could be a predictor of PAF. Accordingly, we were able to show LA size to be associated with PAF, overlapping with the previous findings. 3) On the other hand, the relevant research confirmed that some AF may originate in the atrium and characterize right atrial ectopic onset and right-to-left dominant frequency gradients.[22] Furthermore, mapping and extracting complex fragmentation potentials not only for the left atrium and pulmonary veins but also for the left and right atria may contribute to the success rate in patients with permanent and persistent AF,[23] which suggests that right atrium-triggered AF may deserve more attention compared to left atrial AF. What is more, recent studies have confirmed that right heart disease can also increase the risk of AF.[24-26] Therefore, further clarification of the pathogenesis of AF is needed to bring more insights into the understanding of AF and to offer novel ideas for AF treatment. In addition to secondary right heart dysfunction led by ischemia, cardiomyopathy, or congenital cardiac structural abnormalities, pulmonary vascular remodeling-leading right heart dysfunction is also a right heart disease associated with an increased risk of AF,[24] and its central process in the pathogenesis may be related

to the enlargement of the right atrial cavity caused by pulmonary arterial hypertension (PAH) induced by increased right atrial afterload, tricuspid regurgitation, and right atrial hypertrophy.[25-27] Therefore, we thought that the TAPSE/PASP ratio, which was proven to be closely linked with right heart pathologies in many studies, may be associated with the development of PAF. In this regard, as in our findings, a TAPSE/PASP ratio of <0.67 is likely to signal the presence of PAF.

Limitations

Our research is not free of a few limitations. The single-center nature of the study restrains the generalizability of our findings. Moreover, we included only acute ischemic stroke patients in the study. In this sense, we believe our results may inspire further multicenter research to focus on multiple disorders.

CONCLUSION

Overall, the scholarly community should acknowledge the role of a low TAPSE/PASP ratio (<0.67) in predicting PAF in patients. Thus, it may be helpful to consider the TAPSE/PASP ratio along with the Holter monitoring that is commonly adopted for the diagnosis of PAF.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of theBalıkesir University Clinical Researches Ethics Committee (Date: 05.17.2023, Decision No: 2023-55).

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Prospective examination of Tp-e interval and Tp-e/QT ratio in breast cancer patients receiving radiation therapy

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ABSTRACT

Aims: The aim of this prospective study was to investigate ventricular repolarization using the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in breast cancer patients treated with adjuvant radiotherapy(RT) following systemic chemotherapy.

Methods: The study was designed as a national, single-center prospective study. According to the treatment protocol, electrocardiograms (ECGs) were taken from all patients on their first and last days of RT. Tp-e intervals, Tp-e/QT ratios, and Tp-e/QTc ratios were calculated based on the ECG recordings. The heart doses due to radiation exposure were examined with mean heart dose, V5, V10,V20, and V30 values.

Results: 51 postsurgical patients, who were all treated with AC followed by weekly paclitaxel and had an indication for adjuvant RT, were included in the study. The mean heart dose was observed as median 205 cGy, and the V30 value was 0.01%. When ECG measurements were analyzed, statistically significant increases were observed in Tp-e interval ($p<0.001$), QT interval ($p=0.007$), Tp-e/QT ratio ($p<0.001$), and Tp-e/QTc ratio ($p<0.001$) at the end of RT. Additionally, positive correlations were observed between mean heart dose and post RT Tp-e ($r= 0.770, p<0.01$) and Tp-e/QTc ratio ($r = 0.778, p<0.01$)

Conclusion: When compared to before RT, statistically significant prolongation of Tp-e interval and QT interval and increases in Tp-e/QT ratio and Tp-e/QTc ratio were detected which are thought to be predictive for ventricular repolarization process and ventricular rhythm disorders. In addition, the mean heart dose was positively correlated with Tp-e interval and Tp-e/QTc ratio.

Keywords: Radiotherapy, cardiac toxicity, breast cancer, Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio

INTRODUCTION

Breast cancer is one of the most common types of cancer in women. Today, progress has been made in every field of treatment, from local treatments to chemotherapy and hormonal therapies, from targeted agents to immunotherapies. In light of these developments, personalized treatments are used more effectively in breast cancer, and life expectancy has increased. Consequently, patients now face treatment-related toxicities for longer periods of time during follow-up. Therefore, efforts to reduce unnecessary and/or preventable treatment toxicities continue in every field.

RT is one of the most important parts of multidisciplinary breast cancer treatment, due to its contributions to local control and overall survival. However, in patients who survive long-term, radiotherapy-related cardiac toxicity is one of the most remarkable factors affecting life span. One of the leading mechanisms in radiotherapy-induced cardiac pathogenesis is progressively increasing fibrosis and related functional damage in cardiac subunits. This can include atherosclerotic plaque formations in the vascular wall and related circulatory disorder changes due to reactive inflammation in the microenvironment, decreases in cardiac adipose tissue and decreases in myocardial movement and flexibility due to increased fibrosis, valvular degenerations and rhythmic disorders due to damage to the conduction system with increasing fibrosis acute and chronic pericarditis, and restrictive/constrictive cardiomyopathies.[1,2]

Moreover, on the basis of all this pathogenesis, with the influence of high-energy ionizing radiation at the cellular level, RT may have a disruptive role in the functions of cell membranes containing ion gates, mitochondria-like organelles in the cytoplasm, and the nucleus. On the other hand, a process leading to inhibition of the mitotic cycle and cellular apoptosis may occur with the direct effect of ionizing radiation on biomolecules such as DNA, RNA and signaling molecules. As a result of all these effects, ionizing radiation may cause impairment in signal transmission between myocardial cells.[3-5]

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Electrocardiography (ECG) is created by recording electrical data produced by the cardiac neural conduction system. ECG waves are generated by the electrical current produced when myocardial cells contract as a result of depolarization and relax as a result of repolarization. Structural electrocardiographic changes, such as changes in the height and width of these waves and irregularities in the waves, may reflect subclinical cardiac damage. These wave changes can be helpful in detecting conditions such as rhythm changes, conduction disorders, coronary circulation disorders, electrolyte imbalances, ischemia, and infarction.

The QT interval (QT) and the Tpeak-end interval (Tp-e) which represents the interval between the peak of the T wave (Tpeak) and the end of the wave (Tend), corresponds to the process of transmural distribution and myocardial repolarization.

The QT interval (QT) and the Tpeak-end interval (Tp-e) which is from the top of the T wave (Tpeak) to the end (Tend) correspond to the transmural dispersion and myocardial repolarization process. Prolonged QT and QTc are related with prolonged action potential duration at the cellular level. Various studies have shown that prolonged Tpeak-end interval and increased Tpeak-end/QT and Tpeak-end/QTc ratios may be associated with ventricular rhythm disorders.[6-8] From this point of view, the aim of this prospective study is to evaluate the ventricular repolarization effect of breast radiotherapy using electrocardiographic changes.

METHODS

Ethics

This prospective study was approved by the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (Date: 26.01.2021, Decision No: 311), and the Turkish Medicines and Medical Devices Agency (Date: 02.03.2021, Decision No: 593/08.12.2015). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population Between January 2020 and February 2022, 51 patients, all treated with postoperative AC followed by weekly paclitaxel and adjuvant RT, were included in the study. All patients were analyzed in terms of age, tumor biology, disease stage, applied local and systemic treatments, ECG findings before and after RT, and heart doses due to RT. The American Cancer Committee (AJCC) TNM staging system (8th edition, 2017) was used for staging. Written consent form was obtained from the patients included in the study.

The Exclusion Criteria

The exclusion criteria were administration of neoadjuvant chemotherapy (CT) , administration of any treatment other than adjuvant doxorubicin/cyclophosphamide (AC) followed by weekly paclitaxel, positivity of human epidermal growth factor receptor 2 (HER2), coronary artery disease, arrhythmia, congenital heart disease, heart valve dysfunction, cardiomyopathy, dyslipidemia, history of myocardial infarction, liver or renal function test abnormality, chronic pulmonary disease, hypocalcemia, hypercalcemia, or other serum electrolyte abnormalities, using a pacemaker or cardioverter defibrillator, heart rate greater than 100 beats per minute, heart rate less than 60 beats per minute, ST-T segment changes, branch block on ECG, and use of any medication that affects the cardiac conduction system, such as antiarrhythmics.

Electrocardiographic Measurements

Electrocardiographic recordings were taken from each patient on the first and last day of radiotherapy. The QT interval was obtained from at least six measurements, of which at least three were from the chest leads. Tp-e/QT ratio was calculated from the manually measured electrocardiographic wave and interval changes. All measurements carried out by a single specialist cardiologist. Bazett's formula was used to calculate the QTc interval and Tp-e/QTc ratios were calculated according to the obtained values.

Treatment Protocol

All patients underwent breast cancer surgery. Total mastectomy was performed in cases that not suitable for the breast-conserving approach. Axillary staging with axillary biopsy, sentinel lymph node biopsy, or lymphatic dissection were performed for each patient as clinically necessary. In order to keep the characteristics of the patient population as homogeneous as possible, only the patients who underwent adjuvant doxorubicin/cyclophosphamide (AC) followed by a weekly paclitaxel regimen were included in the study. In patients for whom hormonotherapy was indicated, it started from the end of RT.

Radiotherapy Planning: Simulation, Volume Definition, and Technique

Adjuvant radiotherapy planning was done within the first four weeks after chemotherapy. Computed tomography (CT) simulations were done with a Philips Brilliance (Amsterdam, Switzerland) scanner, with a slice thickness of 3 mm. Patients were simulated in the supine position and immobilized by a breast board. Target volumes and organs at risk (OAR) were delineated using the Varian Eclipse TPS station (Varian Medical

Systems, Sao Paulo), according to the radiation therapy oncology group (RTOG) breast cancer atlas. The spinal cord, heart, ipsilateral lung, contralateral lung, whole lung, and contralateral breast were defined as OAR. Treatment planning was done with three-dimensional conformal radiotherapy (3DCRT) or forward IMRT (intensity-modulated radiotherapy), using field-in-field (FinF) technique. In case dose tolerance limits could not be met, inverse IMRT or VMAT techniques were used. The heart doses were analyzed with V5 (percent volume of the heart receiving a dose of 5 Gy or more), V10, V20, V30, and mean heart dose values. Patient treatments were applied with a linear accelerator device using 6 MV X-rays.

Statistical Analysis

Categorical variables were expressed as numbers and percentages, and continuous variables as median (range). Data distribution was evaluated with the Kolmogorov-Smirnov test and it was observed that the variables were not normally distributed. For this reason, non-parametric Mann-Whitney U test and Chi-square test were used for continuous variables and categorical variables, respectively, in comparisons between groups. Correlations were analyzed using the Spearman correlation test. Statistical analyses were performed using SPSS 25 software (SPSS Inc., Chicago,IL, USA). A probability value of $p<0.05$ was considered significant.

RESULTS

Patient Characteristics

All patients included in the study were female, and the median age was 62 (range 22-82). 90.2% of cases had invasive ductal carcinoma (IDC) histology. 96.1% of the patients were estrogen receptor-positive. 59% of the patients were 50 years or older, and 62.7% were postmenopausal (Table 1). 39.2% of the patients were in the "normal" body mass index (BMI) range (BMI less than 25). 76.5% of the patients had never smoked. All patients underwent breast cancer surgery and adjuvant AC followed by weekly paclitaxel. The numbers of patients who received right and left breast RT were similar. Adjuvant RT details and heart dose values are given in Table 2.

Electrocardiographic Analyses

The median Tp-e interval values before and after RT were 78 and 84; QT interval values were 362 and 367; QTc interval values were 425 and 422; Tp-e/QT rate values were 0.22 and 0.23; Tp-e/QTc rate values were observed as 0.18 and 0.19, respectively. When ECG measurements obtained at the beginning and end of RT were examined, an increase in Tp-e interval ($p<0.001$), QT interval

Table 1. Patient and tumor characteristics

	Patients (n:51, %)
Age	Median; 62 (range 22-82)
<50 yr	21 (41%)
≥50 yr	30 (59%)
Menopausal status	
Premenopause	19 (37.3%)
Postmenopause	32 (62.7%)
BMI (kg/m2)	Median 25 (range 18.7-32)
18.5-24.9	20 (39.2%)
25-29.9	28 (54.9%)
30-34.9	3 (5.9%)
Smoking	
Former /Current smoker	12 (23.5%)
Nonsmoker	39 (76.5%)
Histology	
IDC	46 (90.2%)
ILC	2 (3.9%)
DCIS	3 (5.9%)
Tumor Laterality	
Left breast	26 (51%)
Right breast	25 (49%)
Quadrant	
Upper outer	25 (49%)
Lower outer	8 (15.7%)
Upper inner	5 (9.8%)
Lower inner	1 (2%)
Central	12 (23.5%)
Tumor grade	
I	4 (7.8%)
II	30 (58.8%)
III	17 (33.3%)
Estrogen-receptor status	
Positive	49 (96.1%)
Negative	2 (3.9%)
Ki 67 Status	
<%14	17 (33.3%)
≥%14	34 (66.7%)
Type of breast Surgery	
Breast Conserving Surgery	38 (74.5%)
Mastectomy	13 (25.5%)
T Stage	
Tis	3 (5.9%)
T1	15 (29.4%)
T2	26 (51%)
T3	6 (11.8%)
T4	1 (2%)
N Stage	
N0	27 (52.9%)
N1	17 (33.3%)
N2	5 (9.8%)
N3	2 (3.9%)

Table 2. Adjuvant radiotherapy details

	Patients (n:51,%)
RT Planning Modality	
Forward-IMRT	34 (66.7%)
Inverse-IMRT	17 (33.3%)
Radiotherapy Dose	Median 50 Gy (range 42.5-52)
Radiotherapy Boost	
Yes	37 (72.5%)
No	14 (27.5%)
Axillary RT	
No	24 (49%)
Yes	27 (51%)
SCN+LEVEL III	16 (32.7%)
SCN +LEVEL I-II-III	5 (10.2%)
SCN +LEVEL I-II-III+IMC	4 (8.2%)
Cardiac dosimetric parameters	Median (range)
Mean dose	205 cGy (83-563)
V5	5.8% (0-40)
V10	2.27% (0-10.2)
V20	0.24% (0-8.3)
V30	0.01% (0-7)

(p=0.007), Tp-e/QT ratio (p<0.001) and Tp-e/QTc ratio (p<0.001) were observed (Table 3). Additionally, a positive correlation was observed between mean heart dose and post-RT Tp-e interval (r=0.770, p<0.01, Figure 1) and Tp-e/QTc ratio (r=0.778, p<0.01, Figure 2). There was no statistically significant relationship between other cardiac dosimetric parameters like as V5, V10, V20, V30 and electrocardiographic measurements.

Table 3. Electrocardiographic findings

	Pre –RT (n=51;median)	Post-RT (n=51;median)	p-value
Tp-e interval	78 (56-112)	84 (64-123)	<0.001
QT interval	362 (315-416)	367 (316-451)	0.007
QTc interval	425 (363-487)	422 (364-494)	0.826
Tp-e/QT rate	0.22 (0.15-0.29)	0.23 (0.12-0.50)	<0.001
Tp-e/QTc rate	0.18 (0.13-0.28)	0.19 (0.13-0.49)	<0.001

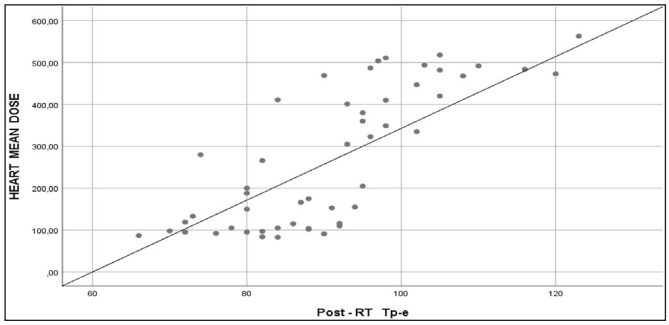

Figure 1. Correlation between post-RT Tp-e and heart mean dose

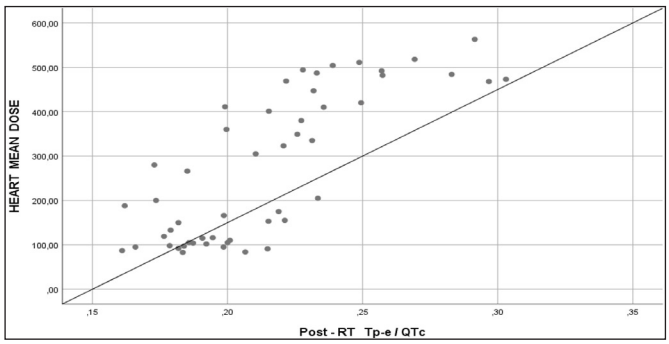

Figure 2. Correlation between post-RT Tp-e /QTc ratio and heart mean dose

DISCUSSION

The present study is one of the rare studies examining the effects of RT on ventricular repolarization in the acute period in patients undergoing RT due to breast cancer.[9] We tried to observe and discuss the acute changes in patient ECGs when the RT was added to the adjuvant therapy following AC plus weekly paclitaxel after breast surgery. Our aim was to observe the acute phase radiation effects on electrical imbalance, intracellular signaling, and action potential duration at the cellular level. In the study, the increases in the Tp-e/QT and Tp-e/QTc ratios and the prolongation of the Tp-e interval and QT interval were statistically significant, which corresponds to the ventricular repolarization process and ventricular rhythm disorders.[1,3,10-14]

We also observed a prolongation of Tp-e interval and an increase in Tp-e/QTc ratio, both of which positively correlated with the mean heart doses.

Many long-term analyses of radiation-associated cardiovascular dysfunction show an increased mortality rate due to ischemic heart disease in the population of patients who received breast RT compared to those who did not.[15-18] Moreover, it has been reported that each Gy increase in the mean heart dose increases the risk of cardiac events by 7.4% in patients undergoing RT for left breast cancer.[16]

RT is indicated in 37% of patients diagnosed with breast cancer; therefore, it is important to examine the pathogenesis of each level of acute change as well as the late effects of this treatment method. In today's complex multimodal treatment of breast cancer, it is difficult to determine the isolated effect of a single modality on the heart. In addition to factors such as the patient's body mass index, dietary habits, family history, smoking, hyperlipidemia, physical activity habits, and comorbidities, the effects of combined treatments converge. Similarly, the acute and chronic effects of each treatment, such as general anesthetic medications, analgesic drugs, combined systemic chemotherapeutic drugs, endocrine treatments, monoclonal antibody treatments, and RT, are observed simultaneously. Although it is a small-scale study, we excluded individuals with coronary artery disease, arrhythmia, congenital heart disease, heart valve dysfunction, cardiomyopathy, dyslipidemia, etc. from the study in order to reduce other comorbidity factors while evaluating acute and subacute electrocardiographic effects.

Gary et al.[19] investigated the effect of the Tpeak-Tend interval prolongation on arrhythmia and cardiac mortality with a meta-analysis involving 155,856 patients. Their results show prolongation of the Tpeak-Tend interval (mean cut-off: 103.3±17.4 ms) was a statistically significant predictive factor for arrhythmia, cardiovascular death, sudden cardiac death, and overall mortality.

Larsen et al.[20] reported electrocardiographic changes such as QTc prolongation, supraventricular and ventricular rhythm abnormalities in the post-treatment period in 134 patients exposed to anthracycline and/or cardiac irradiation during childhood and adolescence (p<0.001). They recommended ECG monitoring as a part of the follow-up protocol for arrhythmia in this group of patients receiving cardiotoxic therapy.

Herman referred to Larsen's study and emphasized that ventricular arrhythmias can be seen in up to 8% of patients treated for childhood tumors, according to studies on patients receiving thoracic RT and anthracycline therapy. Additionally, he emphasized that RT may cause bradycardia due to its effects on the cardiac conduction system, such as in the atrioventricular (AV) nodal area and in the bundle branches. Furthermore, in order to prevent arrhythmias related to cancer treatment, Herman recommended identifying patients with ECG changes before treatment and eliminating other comorbidities that predispose these patients to arrhythmias.[21]

Chen et al.[22] retrospectively evaluated 168 patients treated for pediatric malignancy in terms of cardiotoxicity. In their analysis of the patients' electrocardiographic findings, which were monitored at regular intervals in the patients' follow-up care, they observed that one of 18 patients (6%) who received thoracic RT developed ventricular systolic dysfunction in the acute period after radiotherapy.

Teng et al.[23] drew attention to cardiac autonomic dysfunction due to RT and chemotherapy and reported that cardiac involvement may be related to multifactorial effects, including direct nerve damage. They also pointed out that cardiac autonomic dysfunction may be a precursor to a more common cardiomyopathy and that early detection and elimination can prevent more serious manifestations.

In a prospective study, Gomez et al.[24] investigated the acute cardiac effects of RT in 25 patients exposed to cardiac irradiation due to thoracic RT and found that approximately half of the patients had changes in T and R waves on their post-RT ECGs.

In the European Society of Cardiology (ESC) guidelines, cardiovascular side effects associated with cancer treatment were examined under nine subtitles. They emphasized that QT prolongation may be associated with ventricular arrhythmia and that this side effect may develop due to both acute and chronic toxicity mechanisms. They pointed out that any type of supraventricular arrhythmia may develop in the acute period during or after RT and that sinus node dysfunction and conduction disorder may occur after RT, and this damage may be permanent. Additionally, the guideline recommendations emphasize the importance of regular cardiac monitoring from the beginning of cancer treatment and evaluating QT interval changes in detail.[25]

Thanks to current technological developments, heart doses are minimized through applications such as respiratory monitoring systems, use of prone treatment positions, and partial breast irradiation in breast cancer RT.[9,26] Widespread usage of these techniques and careful reporting of cardiac doses when planning RT will always remain important. Consequently, we aimed to detect breast cancer patients with possible cardiac risk in the early period, to follow them carefully with cardiac monitoring, and to plan preventive treatment by eliminating underlying factors.

Limitations of the Study

The most important limitation predicted at the beginning of the study is that the patients received systemic chemotherapy before RT. As it is known, some chemotherapeutic agents have side effects such as myocardial infarction and arrhythmia that may affect ventricular repolarization. However, as mentioned above, we attempted to observe ventricular repolarization changes in the acute period at the end of RT in the patients, who all received AC followed by a weekly paclitaxel regimen, which is frequently applied in daily practice in the adjuvant treatment setting before RT. Patients receiving neoadjuvant chemotherapy and patients receiving trastuzumab, whose cardiac effects were the subject of a separate study, were not included. Inability to achieve complete homogenization in terms of other factors such as age, menopause status, BMI that may affect ECG findings can be listed among other limitations.

CONCLUSION

In this study, we aimed to draw attention to the subclinical cardiac effects reflected on ECGs in the acute period with the addition of radiotherapy (RT) in the adjuvant setting. During the RT process, clinicians should consider that the detection of Tp-e interval and QT interval changes, which are thought to be predictive of ventricular arrhythmia, may be beneficial in early identification of patients at risk for cardiac morbidity

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (Date: 26.01.2021, Decision No: 311).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

MEDICINE PALLIATIVE CARE

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Which factors are predicting the mortality in patients with COVID-19 in the intensive care unit?

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ABSTRACT

Aims: COVID-19 infection is a global health problem; clinical and laboratory parameters have been developed to predict this disease-related mortality/morbidity. Some of these parameters are clinical parameters, while some are laboratory parameters. This study aims to determine whether Acute Physiology and Chronic Health Evaluation (APACHE) II, Glasgow Coma Scale (GCS), age, presence of comorbidity, and absolute lymphocyte count effectively predict mortality in patients admitted to intensive care unit (ICU) due to COVID-19.

Methods: We have included 108 PCR-positive COVID-19 patients admitted to the ICU between 1 October and 31 November 2020 in our research. Demographic characteristics of all patients, APACHE II values within the first 24 hours of admission to ICU, the GCS, the presence of comorbidity, lymphocyte count during ICU admission, duration of ICU stay, and the mortality rates were recorded.

Results: The average age of 108 individuals evaluated in the study was 67±13.61 years, and 56.5% of the patient group consisted of the geriatric age range. Seventy (64.8%) of the patients were female, eighty-nine (82.4%) patients had at least one comorbidity. In the multivariate analysis, it was determined that lymphocyte value, APACHE II score, and the presence of any comorbidity are independent prognostic factors for mortality when accepted to ICU.

Conclusion: In our study, we have determined that age, APACHE II value, presence of comorbidity, and baseline lymphocyte counts are independent predictors of mortality.

Keywords: Mortality, COVID-19, intensive care unit

INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) epidemic that emerged in Wuhan, China, is a member of the coronavirus family and has affected all world countries and caused a pandemic throughout 2020.[1] According to this infection spread table generated by the SARS-CoV-2 virus, 10-20% of the patients require intensive care unit (ICU).[2] While the disease-related hospital mortality rate is 4.3-11%, the mortality rate among the patients admitted to ICU varies between centers and is around 30-60%.[3,4] In COVID-19 patients admitted to ICU with respiratory failure, clinical deterioration may rapidly deteriorate. Patients are lost due to severe acute respiratory distress syndrome (ARDS) and subsequent multiple organ dysfunction.[5] COVID-19 infection is a global health problem, and an effective scoring system established with clinical and laboratory parameters to predict this disease-related mortality/morbidity has not been defined. Scoring systems developed to predict patients' prognosis during admission to ICU and evaluate the treatment's effectiveness is widely used in non-COVID patients. Acute Physiology and Chronic Health Evaluation (APACHE) II, one of the most commonly used scoring systems, is known to be a successful scoring system in terms of mortality prediction.[6] There is insufficient information that these scoring systems effectively predict mortality in COVID-19 patients, and research on this subject continues. Again, the decrease in the number of lymphocytes in COVID-19 associated viral infection is thought to be the result of direct binding of the virus with angiotensin converting enzyme 2 (ACE2) receptors on lymphocytes and apopytosis caused by a cytokine storm. In a recent meta-analysis published by Lui et al.[7] 35-75% of the patients developed lymphopenia, and it states that

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mortality increased significantly in these patients. Fan et al.[8] reported that a lymphocyte count of <0.6 x10^9/L was associated with a poor prognosis in an analysis of 67 COVID-19 patients during their admission to an ICU.[9]

In this study, we aim to determine which factors effectively predict mortality in patients admitted to ICU due to COVID-19.

METHODS

Study Design and Candidates

This study was conducted in 3rd level ICUs. These intensive care units, where the patients were followed and treated as the 3rd level ICUs, were separated as the COVID-19 ICU due to the pandemic. Patients admitted to the ICU between October 1 and November 31, 2020 were included in our study. After our hospital's ethics committee's approval (protocol number E1/1513/2021; dated 12/07/2023), all patient data were obtained from electronic medical records and patient follow-up forms. All procedures followed were in accordance with the ethical standards (institutional and national) of the committee responsible for human experiments and the 1975 Declaration of Helsinki, revised in 2008.

The demographic characteristics of all patients, APACHE II values within the first 24 hours of admission to ICU, Glasgow Coma Scale (GCS), presence of comorbidity, lymphocyte count during ICU admission, length of stay in ICU, and presence of mortality were recorded.

In this study, while 65 years and over were accepted as advanced age, the average APACHE value for APACHE II was obtained by univariate analysis. As a result of this analysis, it was planned to compare those with APACHE II values of 19 and above and those below. Again, patients with a value of 10 and below for the GCS were accepted as patients in the precoma state. The cut-off value for the baseline lymphocyte count was accepted as 0.8×10^9/L, based on the national COVID-19 science committee guidelines.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (IBM SPSS Inc, Chicago, IL, USA) version 20.0. Descriptive statistics were expressed as mean±standard deviation or median (min-max) for continuous variables and number/percentage for categorical variables. Chi-square test was used for the categorical parameters, and Anova Table Test was used for continuous parameters. Variables with a p-value <0.05 in the univariate analysis were included in the multivariate analysis after the correlation between the factors was determined for exitus. Multivariate Backward Stepwise Cox Proportional Hazard Regression Analysis was used to determine the effects of variables effective on mortality. P-value <0.05 was considered statistically significant for the results.

RESULTS

The average age of the 108 individuals evaluated in the study was 67±13.61 years, ranging from 27 to 89. The geriatric group comprised 56.5% of the patient group. Seventy (64.8%) of the patients were female, eighty-nine (82.4%) patients had at least one comorbidity. There were hypertension in 46 (42.6%) patients, diabetes mellitus in 39 (36.1%) patients, cardiovascular disease in 31 (28.7%) patients, chronic obstructive pulmonary disease in 18 (16.7%) patients, chronic renal failure in 9 (8.3%) patients, history of cerebrovascular disease 8 (7.4%) patients, 8 (7.4%) patients with a history of malignancy, and 4 (3.7%) asthma bronchiale (Table 1).

The study group's median APACHE II value was 19 (range; 1-50), and the median GCS score value was 13.5 (range; 3-15). GCS score value was 10 in 31 (28.7%) patients. When admitted to ICU, the median lymphocyte value was 605×10^9/L and varied between 80×10^9/L and 3910×10^9/L. It was observed that the patients stayed in the ICU for an average of 9.56±7.43 days, 46 (42.6%) patients were discharged from the ICU, and 62 (57.4%) patients died (Table 1).

Table 1. Demographic, clinical, characteristics of patients

Characteristics		Mean±SD	Median (range)
Age (year)		67±13.61	69 (27-89)
APACHE II		20.17±11.55	19 (1-50)
Glasgow coma scale score		11.78±4.14	13.5 (3-15)
ICU length of stay (day)		9.56±7.43	7 (1-39)
Lymphocyte count at ICU admission (x10^9/L)		774.5±589.28	605 (80-3910)
		n	**Percentage**
Geriatric patient	<65 years ≥65 years	47 61	43.5 56.5
Glasgow coma scale score	≤10 >10	31 77	28.7 71.3
Gender	Female Male	38 70	35.2 64.8
Any co-morbidity	Absent Present	19 89	17.6 82.4
Hypertension	Absent Present	62 46	57.4 42.6
Diabetes mellitus	Absent Present	69 39	63.9 36.1
Chronic obstructive pulmonary disease	Absent Present	90 18	83.3 16.7
Asthma bronchiale	Absent Present	104 4	96.3 3.7
Cardiovascular disease	Absent Present	77 31	71.3 28.7
History of malignity	Absent Present	100 8	92.6 7.4
Chronic renal failure	Absent Present	99 9	91.7 8.3
Cerebrovascular disease	Absent Present	100 8	92.6 7.4
Other co-morbidity	Absent Present	79 29	73.1 26.9
Mortality	No Yes	46 62	42.6 57.4

In the univariate analysis, it was seen that age, APACHE II score, GCS score, lymphocyte value when accepted to ICU, presence of any comorbidity determined mortality (Table 2).

Table 2. Factors predicting the mortality in patient with COVID 19 in intensive care unit, univariate analysis

Features		Mortality		P value
		No n (%)	Yes n (%)	
Age [1]	<65 years ≥65 years	30 (63.8) 16 (26.2)	17 (36.2) 45 (73.8)	<0.001
APACHE II [2]	≤19 >19	43 (79.6) 3 (5.6)	11 (20.4) 51 (94.4)	<0.001
Glasgow coma scale score [3]	≤10 >10	3 (9.7) 43 (55.8)	28 (90.3) 34 (44.2)	<0.001
Gender	Female Male	14 (36.8) 32 (45.7)	24 (63.2) 38 (54.3)	0.373
Lymphocyte count at ICU admission (10^9/L) [4]	≤800 >800	24 (32.4) 22 (64.7)	50 (67.6) 12 (35.3)	0.002
Any co-morbidity	Absent Present	13 (68.4) 33 (37.1)	6 (31.6) 56 (62.9)	0.012
Hypertension	Absent Present	31 (50) 15 (32.6)	31 (50) 31 (67.4)	0.071
Diabetes mellitus	Absent Present	35 (50.7) 11 (28.2)	34 (49.3) 28 (71.8)	0.023
Chronic obstructive pulmonary disease	Absent Present	42 (46.7) 4 (22.2)	48 (53.3) 14 (77.8)	0.056
Asthma bronchiale	Absent Present	44 (42.3) 2 (50)	60 (57.7) 2 (50)	0.760
Cardiovascular disease	Absent Present	35 (45.5) 11 (35.5)	42 (54.5) 20 (64.5)	0.343
History of malignity	Absent Present	43 (43) 3 (37.5)	57 (57) 5 (62.5)	0.762
Chronic renal failure	Absent Present	43 (43.4) 3 (33.3)	56 (56.6) 6 (66.7)	0.557
Cerebrovascular disease	Absent Present	43 (43) 3 (37.5)	57 (57) 5 (62.5)	0.762
Other co-morbidity	Absent Present	36 (45.6) 10 (34.5)	43 (54.4) 19 (65.5)	0.302

1: Geriatric age, 2: Median value, 3: The cut-off value for Glasgow Coma Scale Score was selected 10 which is defined comatose patient , 4: The cut-off value for the baseline lymphocyte count was accepted as 0.8×10^9/L, based on the national COVID -19 science committee guidelines. ICU: Intensive Care Unit

Factors associated with mortality were evaluated by correlation in univariate analysis, and it was found that there was only a correlation between the presence of any comorbidity and diabetes mellitus. Therefore, excluding diabetes mellitus, age (≤65 years vs. <65 years), lymphocyte value (≤800×10^9/L vs. >800×10^9/L), APACHE II score (> 19 vs. ≤19, when admitted to ICU), the presence of any comorbidity (present vs. absent), and the GCS score (≤10 vs. >10) for multivariate analysis to determine death. In the multivariate analysis, it was determined that lymphocyte value, APACHE II score, and the presence of any comorbidity are independent prognostic factors for mortality when accepted to ICU. Death increased 76 times in those with APACHE II score >19 (95% Confidence Interval: 10.851-533.783; p <0.001). This ratio was 7 (95% Confidence Interval: 1.520-33.827; p=0.013) for those with a lymphocyte count of ≤800×10^9/L and 8 for those with any comorbidity (95% Confidence Interval: 1.015- 64.151; p=0.048) (Table 3).

Table 3. Factors predicting exitus, multivariate analysis

Factors	Odds ratio	95% confidence interval	P value
Age (≥65 years vs. <65 years) [1]	2.4	0.625-9.212	0.202
Lymphocyte count (≤800×10^9/L vs.>800×10^9/L) [2]	7.171	1.520-33.827	0.013
APACHE II (>19 vs. ≤19) [3]	76.105	10.851-533.783	<0.001
Co-morbidity (present vs. absent)	8.068	1.015-64.151	0.048
Glasgow coma scale score (≤10 vs. >10) [4]	1.487	0.154-14.374	0.732

1: Geriatric age was selected for analysis, 2: The cut-off value for the baseline lymphocyte count was accepted as 0.8×10^9/L, based on the national COVID -19 science committee guidelines. 3: Median value, 4: The cut-off value for Glasgow Coma Scale Score was selected 10 which is defined comatose patient

DISCUSSION

Our primary aim in this study was to evaluate whether age, APACHE II value, presence of comorbidity, GCS, and baseline lymphocyte count were successful in predicting mortality in COVID-19 patients. Our study determined that the baseline lymphocyte value, APACHE II score, and the presence of any comorbidity are independent prognostic factors for mortality.

For many years, many scoring systems have been used in ICUs to predict mortality and morbidity.[10] Among these systems, APACHE II is accepted as the most successful scoring system in predicting mortality in all ICU types and different patient groups.[11,12] In some articles, it has been reported to be successful in COVID-19 patients.[13,14] A study conducted by Zou et al.[15] they stated that the APACHE II value of 17 or above in COVID-19 patients was an independent predictor for hospital mortality. Our study determined that the APACHE II value of >19 and above is an independent risk factor, and death is 76 times more common in these cases. APACHE II scoring, which is calculated by taking the worst values during admission to ICU, acts as an early warning system for physicians' high scores following these cases. These scoring systems are widely used in centers where intensive patient admissions are made during the pandemic, and they are instrumental in planning the treatment process of cases with high APACHE II values.

Although there is not enough information about using the GCS, which is frequently preferred in neurological examination in ICU, in COVID-19 cases, the GCS data can be based on studies using APACHE II since it is a parameter of APACHE II scoring.[16] Our study showed

that GCS being 10 or less has a significant relationship with mortality. In 28.7% of the cases, the GCS was 10 or less, and the mortality was 90.3%.

In the COVID-19 outbreak, it was observed that mortality rates were different in different age groups.[17] It is observed that pulmonary physiology, pathology, and functions change in the presence of lung infection with aging. Therefore, in elderly individuals, response to the disease and tolerability deteriorate, and the mortality rate increases.[18] Studies on advanced age COVID-19 patients have shown an increased risk of death.[19-22] In our study, 56.5% of the cases were 65 years old and above, and the mortality rate in these cases was significantly higher compared to patients aged 65 years or younger.

The presence of concomitant diseases in COVID-19 cases complicates the clinical picture. In their study by Chen et al.[23] in which they evaluated the epidemiological and clinical characteristics of the cases they followed up with COVID-19 viral infection, they determined the presence of chronic disease in 51% of the cases and stated that cardiovascular, cerebrovascular disease, and diabetes mellitus were the most common accompanying diseases. They indicate in their research that mortality is higher in cases with comorbidity.[24] In our research, we observed that 82.4% of our cases had at least one concomitant disease. The most common accompanying disease was hypertension (42.6%), followed by diabetes mellitus (36.1%). In our study, unlike Chen et al., the accompanying cardiovascular disease rate was in the 3rd rank with 28.7%. While any comorbidity's presence increased the risk of death eight times, mortality was found to be statistically significantly higher in patients with diabetes mellitus compared to those without diabetes mellitus.

The absolute value of lymphocytes decreases in COVID-19 associated viral infection. The reason for this decrease is related to the effect of 2019-nCoV on SARS-CoV lymphocytes, especially T lymphocytes. Virus particles spread to the respiratory mucosa and initiate a cytokine storm in the body. This situation stimulates the immune system and causes changes in peripheral white blood cells and immune cells such as lymphocytes. Some patients progress rapidly and pass away by developing ARDS, septic shock, and multiple organ failure. For this reason, early detection and timely treatment of critical cases are vital. The decrease in the absolute lymphocyte count during admission to ICU is a laboratory parameter that supports clinicians' diagnosis during the diagnosis of COVID-19. In comparison, Huang et al.[25] stated that their absolute lymphocyte count was $<1.0\times10^9$/L in 63% of their patients, Fan et al.[8] showed that absolute lymphocyte count $<0.6\times10^9$/L had a significant correlation with mortality. In our study, when we evaluated the mortality relation of absolute lymphocyte count $<0.8\times10^9$/L, we determined that lymphocyte count $<0.8\times10^9$/L was an independent predictor for mortality. Absolute lymphocyte count $<0.8\times10^9$/L increased the risk of death seven times.

Frater et al.[26] state that there is some geographic variation in the percentage of COVID-19 patients presenting with lymphopenia in their article evaluating COVID-19 and clinical, hematological laboratory findings. For example, an article from Singapore reporting several COVID-19 patients describes a much lower percentage of lymphopenia patients, as in a retrospective analysis of COVID-19 patients from Zhejiang Province, located ~450 miles from Wuhan.[8,27] In contrast, in studies reported from Italy, lymphopenia is common in most patients admitted to the emergency room.[28] The reasons for these and similar discrepancies are unclear, although they are probably multifactorial. Due to viral genomic mutations, it is possible that the immunological response to the virus will change as the pandemic spreads to other countries. Another possibility is that testing patients is not uniform, and the degree of lymphopenia can vary depending on the time of admittance. In our study, we have observed that 74 of 108 patients had an absolute lymphocyte value $<0.8\times10^9$/L.

There were some limitations in our study. The first is that it is a retrospective study, and the second is that there is no long-term (28 days or 6 months) data when determining ICU and hospital mortality. Besides, we think that further studies should be conducted that comparative studies of baseline absolute lymphocyte count with data from different countries may help determine the cut-off value for lymphopenia.

CONCLUSION

In our study, we determined that age, APACHE II value, presence of comorbidity, and initial lymphocyte count are independent predictors of mortality. We concluded that studies with more patients and other clinical / laboratory data related to COVID-19 would be beneficial.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the University of Health Sciences, Ankara City Hospital Ethics Committee (Date: 12/07/2023, Decision No: E1/1513/2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Original Article

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Non dipping pattern frequency and metabolic syndrome relationship according to two different metabolic syndrome diagnostic methods in newly diagnosed hypertensive individuals

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ABSTRACT

Aim: The literature presents conflicting data regarding whether the non dipping pattern (NDP) in patients with metabolic syndrome (MS) compared to those without. In our study, we aimed to investigate the MS effect of the NDP in individuals with hypertension.

Methods: This prospective study included 117 newly diagnosed hypertensive patients (79 women and 38 men) who were not receiving any anti-hypertensive treatment. MS was evaluated according to the currently used the US National Cholesterol Education Programme Adult Treatment Panel-III definition criteria (MS-ATP-III) and a new diagnostic scoring method (MS-Score). NDP defined, nocturnal blood pressure (BP) fell by <10% from daytime BP

Results: The mean age of the patients who met the MS-ATP-III criteria was 53.9+8.1 years. The prevalence of the MS-ATP-III among the study population was 60.6%. The NDP frequency was similar in patients with and without MS-ATP-III, high MS-Score and low MS-Score group (respectively; 44.8%, 47.5%, p=0.79, 44.7%, 46.9%, p= 0.9). The reverse dipping pattern (RDP) frequency was higher in patients with MS-ATP-III compared to those without MS (13.8% and 2.5%, p=0.021), RDP was 10.8% in the high MS-Score group and 8.2% in the low MS-Score group (p=0.66). The LDL (mg/dL) values were higher in those with NDP compared to those without (142.6+32.2, 125.5+28.9, p=0.008).

Conclusion: Despite the high prevalence of MS among newly diagnosed hypertensive patients, the prevalence of NDP does not show a different distribution in patients with MS in both the MS-ATP-III and MS-Score method.

Keywords: Hypertension, non-dipping pattern, metabolic syndrome, reverse dipping pattern, metabolic score

INTRODUCTION

Metabolic syndrome (MS) is a cluster of factors that can increase the risk of developing cardiovascular disease, coronary artery disease, cardiovascular mortality and stroke.[1-4] In addition, a relationship between MS and clinical finding indicating organ damage, such as left ventricular hypertrophy, diastolic dysfunction and microalbuminuria, has been reported.[5-8] The normal circadian blood pressure pattern is characterised by a decrease of 10%–20% in night-time blood pressure levels compared to the daytime levels and is called the dipping pattern (DP). Various researchers have individually defined the non-dipping pattern (NDP) as a reduction of less than 10% in night-time systolic, diastolic or both blood pressure measurements.[9,10] In essential hypertensive patients, as in normotensive individuals, blood pressure levels similarly increase in the early morning hours and decrease during sleep at night. However, in some hypertensive patients, blood pressure may not decrease at night during sleep, or it may decrease slightly or even show some increase.[9-11] In the diagnosis and evaluation of arterial hypertension (HT), ambulatory blood pressure monitoring (ABPM) has been recognised as a better technique compared to office blood pressure measurement, and it works automatically by providing multiple measurements of daily activity and sleep. Consequently, it presents 24-hour (24-h) diurnal blood pressure changes.[11,12] The NDP in blood pressure may be associated with an autonomic nervous system disorder which is characterised by a decrease in parasympathetic system activity.[13] Many previous studies evaluating the relationship between the NDP in blood pressure and target organ damage have shown that the NDP is an independent predictor of left ventricular hypertrophy,

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renal dysfunction, carotid artery stenosis disease and future cardiovascular events.[7,14,15] In addition, many studies have associated the NDP with increased cardiovascular mortality and morbidity.[16,17]

Previous studies have reported controversial results regarding the relationship between MS and the disruption of the diurnal blood pressure pattern. In some of these studies, the rate of NDP and office and ambulatory blood pressure levels were significantly higher in hypertensive patients with MS.[18-21] In some studies, no relationship was found between MS and NDP.[22-25]

In this study, we aimed to investigate the circadian changes in blood pressure, especially the rate of NDP in treatment-naive hypertensive patients with and without MS.

METHODS

Patients who applied to the general internal medicine outpatient clinic between November 2008 and January 2009 were included in the study.

Inclusion Criteria

Patients who were at least 30 years old and were not receiving any anti-hypertensive treatment were included in the study.

Age-and gender-matched patients with untreated HT and without MS formed the control group.

Exclusion Criteria

Patients who were pregnant, were suffering from any chronic disease, had a history of HT treatment, under 30 years of age, suspicion of secondary HT (for example those with hypokalaemia) and refused to participate in the study were excluded. Patients who had previously taken any medication; oral contraceptives, antidepressants or corticosteroids, etc. were excluded from the study. None of the patients in the study were breastfeeding.

Study Design and Work Plan

For MS diagnosis, the US National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP III) diagnostic criteria were used.[26] In addition to HT, at least two of the following four criteria were sought for diagnosis; I. Abdominal obesity (waist circumference >102 cm in men, >88 cm in women), II. High triglycerides (>150 mmol/L), III. Low High-density lipoprotein (HDL) cholesterol (<40 mol/L in men, <50 mol/L in women, IV. Impaired fasting glycaemia (fasting plasma glucose [FPG] >110 mg/dL, or previously diagnosed type 2 diabetes mellitus). FPG, total cholesterol, low-density lipoprotein cholesterol (LDL) cholesterol, HDL cholesterol and triglyceride levels, which were obtained from the outpatient clinic observation files.

Anthropometric measurements, waist circumference (accepted as the narrowest diameter between the arch costa and spina iliaca anterior superior), weight and height were measured, and the body mass index (BMI) was calculated (in kg/m²).

In addition, patients were classified according to the metabolic score (MS-Score) described by Macchia and colleagues[27] scoring is as follows; Male 3 points, age (year) >50 4 points, HT 2 points, BMI (kg/m²); <26 0 points, 26-27 3 points, >28 6 points, triglycerides (mg/dL); 100-159 5 points, 160-199 7 points, >200 9 points, HDL blood cholesterol (mg/dL); >50 0 points, 30-49 3 points, <30 5 points, FPG (mg/dL); <80 0 points, 80-89 5 points, 90-99 10 points, 100-109 16 points, >110 28 points, as high MS-Score if >28 points and low MS-Score if <28 points.27 According to NCEP-ATP III (MS-ATP III) and MS-Score, patients were defined as MS-ATP III (-) and low MS-Score group I, MS-ATP III (+) and low MS-Score group II, MS-ATP III (-) and high MS-Score group III, and finally MS-ATP III (+) and high MS-Score group IV.

For the patients deemed eligible to be included in the study, blood pressure was measured three times a week according to the 2007 ESH and 2008 ESC.[28,29] Before the blood pressure measurement, it was ensured that the patients had rested for at least 5 min and had not consumed coffee, tea or tobacco within half an hour. Systolic blood pressure and diastolic blood pressure were first measured in the non-dominant arm and 2 minutes later in the other arm according to Koroktoff sounds using a mercury sphygmomanometer, in the sitting position and the mean values were recorded. The mean of the three measurements within a week was considered the blood pressure level. Those with mean arterial blood pressure, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg considered HT and included in the study. Afterwards, the patients were fitted with an ambulatory blood pressure device, and those with the 24-h mean blood pressure >130/80 mmHg, daytime mean blood pressure >135/85 mmHg, night-time mean blood pressure >120/70 mmHg, systolic and/or diastolic blood pressure were considered hypertensive. Patients were asked to sleep in the night interval and it was checked with the patients' declaration.

The non-dominant arm and the Watch BP03 device were used for 24-h blood pressure measurement in all patients. The blood pressure monitor was set to

read at 20-min intervals until 07:00–23:00 and at 30-min intervals until 23:00–07:00. All participants were encouraged to continue their routine activities upon leaving the hospital. Information on the mean systolic and diastolic blood pressure levels and heart rate for 24-h during both daytime and night-time was obtained from the records of the ambulatory blood pressure measuring device.

Nocturnal dipping is defined as a 10%–20% decrease in night-time mean systolic blood pressure compared to the daytime value. When this decrease is <10%, we define it as the NDP, and when it is >20%, we define it as extreme DP; if the night-time mean systolic blood pressure increases compared to the daytime value, it is considered as RDP.[9,10]

The IBM® Statistical Package for the Social Sciences (SPSS) statistics programme was used for the statistical evaluation of the data. After the normal distribution was determined t-test was used for comparing the normally distributed data, and a Mann–Whitney U test was conducted to compare non-normally distributed data. In the data comparison, Chi-square was used comparing the ratios, a p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 117 patients, 79 female and 38 male, were identified as meeting the inclusion criteria. The mean age of the patients was 51.3+10.0 years. The prevalence of the MS among the study population was 60.6% (71) and the sex-specific prevalences were 47.4% (53) and 67.1% (18) among female and male patients respectively (p=0.041). The mean age of patients who met the MS-ATP III criterion was 53.9+8.1 years. The demographic characteristics of the patients are listed in Table 1.

NDP

While the parameters such as age, waist circumference, BMI, triglycerides and FPG were similar in patients with NDP compared to those without (Table 2), the LDL (mg/dl) values were found to be lower in those with NDP (Table 2).

The NDP frequency was 51.0% in patients with a BMI (kg/m²) below 30 and 56.5% in those with a BMI above 30, and the two groups were found to be similar (p=0.59).

When the patients were grouped into subgroups according to gender, the NDP frequency was found to be the same in both men and women with and without MS-ATP III (p=0.46, Figure 1.).

Table 1. Characteristics of patients with and without MS

	MS-ATP III (+) (n=71)	MS-ATP III (-) (n=46)	p
Age (years)	53.9+8.1	49.3+9.9	0.007
Body mass index (kg/m²)	31.3+4.7	28.7+4.7	0.003
Waist circumference (cm)	103.1+10.4	97.4+9.4	0.003
Total cholesterol (mg/dL)	201.3+38.2	204.6+40.9	0.7
Triglyceride (mg/dL)	160.0* (69.0-442.0)	113.5* (89.3-138.3)	<0.001
HDL cholesterol (mg/dL)	41.5+9.0	49.5+9.0	<0.001
LDL cholesterol (mg/dL)	135.9+30.5	130.0+32.4	0.34
Fasting blood glucose (mg/dL)	101.7+14.3	91.6+8.8	<0.001
24 hour average systolic blood pressure (mmHg)	136.1+11.2	124.5 + 13.3	<0.001
24 hour average diastolic blood pressure (mmHg)	81.9+7.2	77.5+8.6	0.005
Awake average systolic blood pressure (mmHg)	140.0+10.5	128.6+14.5	<0.001
Awake average diastolic blood pressure (mmHg)	85.2+7.2	80.9+9.3	0.008
Asleep average systolic blood pressure (mmHg)	125.5+15.1	113.4+13.9	<0.001
Asleep average diastolic blood pressure (mmHg)	73.7+9.9	70.4+9.7	0.092
24 h average pulse pressure (mmHg)	54.1+9.0	47.0 + 9.1	<0.001
Awake pulse pressure (mmHg)	54.7+9.1	47.7+9.9	<0.001
Asleep pulse pressure (mmHg)	40.3+14.7	32.5+12.1	0.005
NDP frequency (%)	44.8	47.5	>0.79

MS-ATP III: Metabolic syndrome according to the National Cholesterol Education Programme Adult Treatment Panel III, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, NDP: Non dipping pattern, *since it does not show normal distribution, it is given as median and interquartile range of 25–75 percentiles.

Table 2. Demographic characteristics by dipping pattern and non-dipping pattern

	NDP (n=54)	DP (n=63)	p
Age (years)	52.6+9.5	53.2+8.6	0.56
Body mass index (kg/m²)	31.6+4.9	31.3+5.3	0.83
Waist circumference (cm)	103.0+ 8.5	102.3+11.3	0.88
Total cholesterol (mg/dL)	202.7+38.2	208.8 + 40.4	0.72
Triglyceride (mg/dL)	153.7* (98.5-182.0)	143.0* (108.5-178.0)	0.63
HDL cholesterol (mg/dL)	40.6+11.7	46.6+11.7	0.79
LDL cholesterol (mg/dL)	126.3 + 28.6	141.4+32.9	0.008
Fasting blood glucose (mg/dL)	95.8+12.5	98.6+15.6	0.53

DP: Dipping pattern, NDP: Non dipping pattern,HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, *since it does not show normal distribution, it is given as median and interquartile range of 25–75 percentiles.

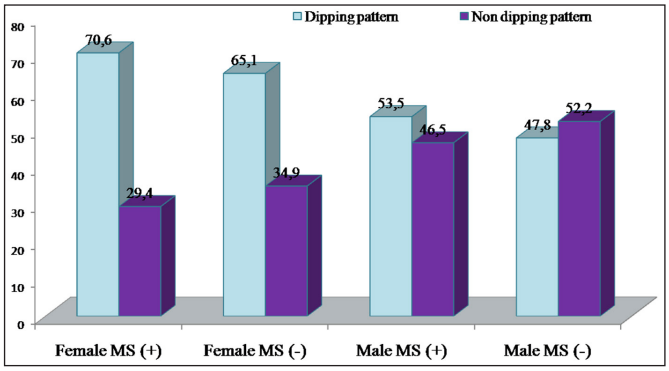

Figure 1. Non dipping pattern frequency according to gender and metabolic syndrome (MS), with and without MS equal distribution for both genders is observed (Female p=0.66, male p=0.9).

The NDP frequency was 50% in patients who did not meet any of the metabolic ATP III diagnostic criteria other than HT, 42.9% in those who met one criterion other than HT, 40.9% in those who met two criteria other than HT, 33.3% in those who met three criteria other than HT,39.1% in those who met four criteria thus, the differences were not significant.

RDP

The RDP frequency was higher in patients with MS-ATP III compared to those without MS-ATP III (13.8% and 2.5%, respectively; p =0.021). While the RDP was seen as 13.5% in men, no RDP was observed in women (p =0.028). When the patients were classified as below and above 30 according to their BMI (kg/m²), the RDP was 2% in those below 30 of BMI and 17.4% in those above 30 BMI (p=0.009).

Extreme DP

Extreme DP was detected as 10.3% in patients with MS-ATP III and 10.0% in those without MS-ATP III; the two groups were similar. In addition, it was found to be 9.1% in women, 12.5% in men, 7.8% in those with a BMI below 30, 13% in those with a BMI above 30, 9.1% in those under 45 years of age and 14.3% in those above 45 years of age. The groups were found to be similar. Patients with extreme DP were also found to be similar in age, BMI and metabolic parameters compared to those without DP.

According to the MS-Score

The characteristics of the patients according to their MS-Score are shown in Table 2. The frequency of NDP was similar in the group with high and low MS-Score (Table 3). In addition, when group I was compared with group IV in terms of NDP frequency, it was also similar (Figure 2). The frequency of RDP was 10.8% in the high MS-Score group and 8.2% in the low MS-Score group (p=0.66).

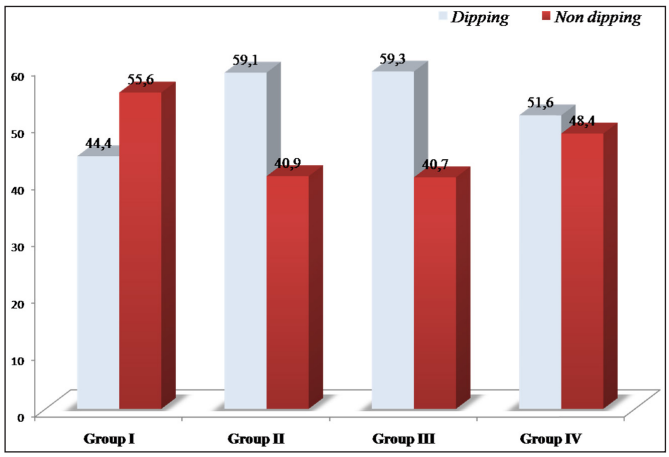

Figure 2. Non dipping pattern frequency according to both MS diagnostic methods, non dipping pattern is found to be similar distribution in groups (from I to IV).

Table 3. Characteristics of patients with high MS-Score and low MS-Score

	MS-Score high (n=54)	MS-Score low (n=62)	p
Age (years)	54.2+7.0	49.1+11.3	0.004
Female/Male (n)	33/21	46/16	0.29
Body mass index (kg/m²)	31.9+4.4	28.8+4.3	<0.001
Waist circumference (cm)	104.6+10.7	96.8+9.8	<0.001
Total cholesterol (mg/dL)	191.0+37.1	214.3+38.2	0.011
Triglyceride (mg/dL)	153.5* (69.0-442.0)	115.0* (48.0-341.0)	<0.001
HDL cholesterol (mg/dL)	42.1+8.1	46.9+11.1	0.009
LDL cholesterol (mg/dL)	131.9+26.5	135.9+35.8	0.5
Fasting blood glucose (mg/dL)	107.6+11.8	88.9+7.6	<0.001
24 hour average systolic blood pressure (mmHg)	134.9+13.9	128.6+12.3	0.017
24 hour average diastolic blood pressure (mmHg)	82.4+7.7	78.1+7.9	0.005
Awake average systolic blood pressure (mmHg)	138.6+13.5	132.5+12.9	0.018
Awake average diastolic blood pressure (mmHg)	85.5+7.4	81.4+8.4	0.008
Asleep average systolic blood pressure (mmHg)	1245+164	117.9+14.9	0.032
Asleep average diastolic blood pressure (mmHg)	74.1+10.3	70.9+9.6	0.10
24 h average pulse pressure (mmHg)	52.4+10.2	50.6+9.2	0.32
Awake pulse pressure (mmHg)	53.1+10.3	51.3+9.8	0.36
Asleep pulse pressure (mmHg)	38.9+14.4	36.2+14.2	0.34
NDP frequency (%)	44.7	46.9	0.9

MS-Score: Metabolic score described by Macchia and colleagues [27], HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, NDP: Non dipping pattern,*since it does not show normal distribution, it is given as median and interquartile range of 25–75 percentiles.

DISCUSSION

In our study, we found that the prevalence of MS was high in newly diagnosed hypertensive patients who were not receiving any anti-hypertensive treatment. There was no difference in NDP between the MS and non-MS groups. When we investigated the relationship between MS and non-dipping blood pressure by comparing different MS definitions, the frequency of NDP was similar between patient groups in both different MS diagnostic methods. The frequency of RDP was higher in patients with MS-ATP III, but not in those with high scores according to MS-Score.

One of the main results of our study is that the frequency of the non-dipping blood pressure pattern was not higher in patients with MS-ATP III. Cuspidi et al.[5,22] Bastos et al.[23] and Foss et al.[22] found that the 24-h average systolic blood pressure (ASBP), awake average systolic blood pressure (AASBP) and asleep average systolic blood pressure (AsASBP) levels were similar for the patients with and without MS.[5,22-24] In the same studies,

the NDP frequency was found to be similar in patients with and without MS.[5,22,23,24] Unlike previous studies, Mancia et al.[25] found that systolic and diastolic blood pressure measurements performed in the office, at home and in ambulatory care for patients with MS were higher than those without MS, while the diurnal variation between wakefulness and night-time was preserved.[25] We observed similar results in our study, where ASBP, AASBP and AsASBP values were higher in patients with MS-ATP III, but the diurnal blood pressure difference was the same between the two groups. A study group of 2,045 non-diabetic patients with a mean age of 49.4 years, who had not received antihypertensive treatment before, was examined by Ayala et al.[18] who found that the 48-h mean systolic/diastolic blood pressure, daytime waking mean systolic or diastolic blood pressure, night-time mean systolic blood pressure, 48-h mean pulse pressure, wakefulness mean pulse pressure and night-time mean pulse pressure were higher in patients with MS than in those without MS.[18] In this respect, our study is similar to Ayala et al's[18] study but differs in that we found the NDP frequency not to be higher in the patient group with MS-ATP III. One of the largest-scale studies that found an association between MS and NDP is the study by Ayala et al.[18] their work is in some aspects different from our work. The frequency of male participants was significantly higher in patients with MS, as a result, the reason for the lower frequency of NDP in patients with MS in the study of Ayala et al.[18] may be that the two groups were not matched in terms of age and gender.[18]

In addition, we found that pulse pressure was higher in patients with MS-ATP III . High pulse pressure is detected when systolic pressure rises or diastolic pressure falls. Epidemiological studies have shown that high pulse pressure is associated with increased systolic HT and cardiovascular events.[30,31] For example, Blacher et al.[31] reviewed three independent meta-analysis studies: The European Group Study of High Blood Pressure in the Elderly (n=840), The European Study of Systolic Hypertension (n=4695) and The Systolic Hypertension Study in the Chinese Population (n=2394).[31] The results of these meta-analyses revealed that a 10 mmHg increase in pulse pressure led to a 13% increase in all coronary events and a 20% increase in cardiovascular mortality. In the Framingham study population (middle and advanced age groups) investigated by Franklin et al.[32] SBP and pulse pressure were found to be positively associated with cardiovascular mortality and negatively correlated with diastolic blood pressure.[32] In addition, for the same age groups, the study found that cardiovascular mortality decreased in patients with high DBP values. However, pulse pressures were similar according to MS-Score, which may be due to the fact that MS-Score are mostly used for diabetes mellitus prediction or that MS-Score contain different epigenetic type, there are gaps in this field and need to be clarified with controlled studies.

Another finding of our study is that the RDP is more common in patients with MS-ATP III than in those without. Yan et al.[33] found that; MS was associated with RDP in men (but not women). In another study, Yan et al.[34] revealed that lacunar infarct and RDP are related. Chen et al.[35] observed that small vessel disease is associated with RDP frequency in patients with HT. Kim et al.[36] found that the RDP is associated with mortality. Cuspidi et al.[37] in a meta-analysis investigating the RDP and subclinical cardiac organ damage, found that the left ventricular mass index is higher in the RDP than in the DP and NDP. On the other hand, the frequency of RDP was similar between those with high MS-Score and those with low MS-Score. Again, it is not easy to explain the reason for this situation. The higher frequency of RDP in MS-ATP III patients may be a coincidental finding due to the small sample size and this effect may disappear as the sample size increases. Alternatively, the frequency of RDP may be higher in MS-ATP III and there may be no difference in RDP between high MS-Score and low MS-Score, reflecting different epigenetic types of MS.

Our study has some weaknesses. First, one weakness of our study may stem from the small sample size of the patients; therefore, we may not have been able to detect some relationships. Another weakness is that we did not investigate end organ damage. Finally, the fact that power analysis was not performed while designing the study may have caused some relationships not to be detected. MS is a cluster of risk factors for atherosclerotic diseases. However, patients with MS seem to have a higher atherosclerotic risk than the risks posed by these factors separately; larger prospective studies are needed to reveal this.

CONCLUSION

On one hand, the NDP frequency does not show a different distribution in patients with MS in both diagnostic methods; on the other hand, the RDP is found to be higher in patients with MS ATP III, but not in high MS-Score. As a result, no effect of MS on blood pressure changes during the day was detected.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the İstanbul No:1 Clinical Researches Ethics Committee (Date: 10.11.2009, Decision No: B-007).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Excerpt from journals;

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Excerpt from the book;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Excerpt from the book, which is the only author and editor;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams & Wilkins; 1996: 46-60.

Excerpt from the book with multiple authors and editors;

Schulz JE, Parran T Jr.: Principles of identification and intervention. In: Principles of Addicton Medicine, Graem AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams & Wilkins; 1998: 1-10.

If the editor is also the author of the chapter in the book;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Excerpt from PhD/Undergraduate Thesis;

Kilic C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

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Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into the family market in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

For other reference styles, see "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References".

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