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Editöryal İletişim
Hacettepe Üniversitesi
Tıp Fakültesi Dekanlığı
06100 Sıhhiye - Ankara
E-posta: editor@actamedica.org

Yayıncı
Hacettepe Üniversitesi
Tıp Fakültesi Dekanlığı
06100 Sıhhiye - Ankara
Telefon: 0 312 305 10 80
Belgeç (faks): 0 312 310 05 80
E-posta: tipmaster@hacettepe.edu.tr

Yayıncılık Hizmetleri
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Hacettepe Medical School
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E-mail: editor@actamedica.org

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Hacettepe University
Hacettepe Medical School
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Phone: +90 312 305 10 80
Fax: 0 312 310 05 80
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ORIGINAL ARTICLE

Sleep medicine practices in pediatric patients during the COVID-19 pandemic

Birce Sunman[1]
ORCID: 0000-0001-9818-8782

Nagehan Emiralioğlu[1]
ORCID: 0000-0002-1405-8401

Beste Özsezen[1]
ORCID: 0000-0002-0052-8361

Dilber Ademhan Tural[1]
ORCID: 0000-0002-0334-6336

Halime Nayir Büyükşahin[1]
ORCID: 0000-0002-6909-7993

İsmail Güzelkaş[1]
ORCID: 0000-0001-7628-7253

Ebru Yalçın[1]
ORCID: 0000-0002-7325-1981

Deniz Doğru[1]
ORCID: 0000-0001-9931-9473

Nural Kiper[1]
ORCID: 0000-0003-1261-7393

Uğur Özçelik[1]
ORCID: 0000-0003-1587-5216

[1] Department of Pediatric Pulmonology, Hacettepe University Faculty of Medicine, Ihsan Dogramaci Children's Hospital, Ankara, Türkiye.

Corresponding Author: Birce Sunman
E-mail: brchmz@gmail.com

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ABSTRACT

Objectives: The COVID-19 pandemic required precautions for infection control in sleep centers. Our aim was to assess the impact of the COVID-19 pandemic on sleep medicine practices.

Methods: Data of patients undergoing polysomnography and positive airway pressure titration studies prior to (2019) and during the pandemic (2020) were analyzed. In addition, the effect of taking appropriate precautions and performing SARS-CoV-2 polymerase chain reaction testing on the safety of sleep medicine practices was investigated.

Results: The median age of the patients who underwent sleep studies (polysomnography + positive airway pressure titration studies) in 2019 was 7 (2.5-11.5) years (164 male, 147 female), whilst it was 9 (4-12) years (127 male, 84 female) in 2020. During the outbreak, the frequency of sleep studies increased from 3% (311 tests/10068 total number of outpatient visits in 2019) to 3.7% (211 tests/5666 in 2020). In contrast, the frequency of positive airway pressure titration studies declined from 31.8% (99 positive airway pressure titration studies/311 sleep studies) to 21.8% (46 positive airway pressure titration studies/211 sleep studies) in 2020 compared to 2019. Down syndrome was found to be the most common indication both in 2019 (20.9% of all tests) and 2020 (13.7%).

Conclusions: Polysomnographies were performed at a high rate despite the pandemic. However, positive airway pressure titration studies were avoided except for urgent indications because of the potential for aerosolization. In this study, it was shown that sleep studies can be performed safely when necessary precautions are taken.

Keywords: COVID-19, children, sleep study, polysomnography.

INTRODUCTION

In late December 2019, unusual pneumonia cases caused by a new coronavirus originated in Wuhan city of China. The existence of a new epidemic was reported to the World Health Organization (WHO) and announced to the world on December 31st, 2019 [1]. On February 11th, 2020, WHO announced that the disease caused by this new coronavirus was called "COVID-19", which stands for "Coronavirus disease 2019". The epidemic that started in the People's Republic of China rapidly spread globally and was declared a pandemic on March 11th, 2020 [2].

The virus is now known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 caused by this virus is a highly infectious disease leading to high morbidity and mortality. Transmission of SARS-CoV-2 from person to person occurs by respiratory droplets containing the virus particles, and via surfaces contaminated by respiratory droplets or other secretions from an infected person [3-5]. Another route is airborne transmission by aerosols [6]. COVID-19 is transmitted by both symptomatic patients and asymptomatic carriers [7].

The first COVID-19 case in Turkey was reported on March 11th, 2020, and it has spread rapidly in our country since this date. In order to curb the pandemic, certain measures such as restricting the use of places of social interactions, postponing various scientific and cultural meetings, prohibiting transportation between cities, cancellation of flights and installing a curfew for the elderly and children have been taken, additionally, non-urgent hospital admissions were likewise restricted. The field of sleep medicine as well as other medical practices and healthcare systems were heavily affected owing to the social distancing measures taken during the pandemic.

Polysomnography (PSG) is the gold standard for the diagnosis of several sleep disorders. It is also used to eval¬uate abnormal sleep-related movements and behaviors. PSG is generally performed in sleep laboratories and requires close and prolonged patient-technician contact [8]. Some phases of the PSG are not suitable for the patient to wear a mask and in these situations, the sleep technician who is in close contact with the patient is potentially exposed to droplets and aerosol particles. In addition to diagnostic PSG, sleep studies are also carried out on patients who require noninvasive ventilation (NIV) therapy such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BPAP) ventilation. In children on chronic positive airway pressure (PAP) support, follow-up PSG is performed to determine whether pressure requirements have changed [9]. NIV has been listed as a high-risk aerosol generation procedure by WHO and it is recommended that airborne precautions in combination with contact precautions are used when performing aerosol-generating procedures [8, 10]. Therefore, sleep medicine practices need to be adapted according to the current pandemic measures.

The purpose of this study was to determine how the social and medical measures taken to prevent the spread of the COVID-19 pandemic affected the sleep medicine in our tertiary center and to compare how sleep medicine procedures and indications during the pandemic have changed compared to the previous year.

METHODS

Study design

This observational descriptive study was conducted at the pediatric pulmonology department of our tertiary referral children's hospital between January 2019 and April 2021. The pre-pandemic period which included 14 months from January 2019 to February 2020 was defined as the '2019' period. Whereas the COVID-19 pandemic period included 14-months from March 2020, when the first case was detected in Turkey, to April 2021 and was defined as the '2020' period. Pediatric patients between 0-18 years with sleep disorders as well as other lung diseases are followed up at our center. Patients with a range of diagnoses such as genetic disorders, neuromuscular disorders, metabolic disorders, muscular dystrophies, musculoskeletal disorders, obesity, epilepsy and other rare diseases who underwent sleep studies were included in the study. The total number of annual outpatient department visits between 2019 and 2020 were recorded. Data of patients undergoing PSG or PAP titration studies both prior to and during the

pandemic were extracted from the medical records of the sleep laboratory. Indications of the sleep studies before and during the pandemic were compared.

All patients included in the study underwent type 1 PSG (Alice 6, Philips, USA). PSG consists of an electroencephalogram (4 channels, parietal and occipital), electrooculography (2 channels, right and left), electromyography (tibialis anterior and submandibular), electrocardiogram, oronasal airflow sensor, chest and abdominal movement sensor, body position sensor, snoring microphone, capnometer and a pulse oximeter. Simultaneous video recording was performed by a trained sleep laboratory technician. During PAP titration full PSG monitoring with flow, pressure, leak signals in addition to video and audio signals were recorded. PSG records were evaluated according to the standards of the American Academy of Sleep Medicine (AASM) for children. Pediatric scoring criteria was used for our patients who were under the age of 18 [11]. Apnea-hypopnea index (AHI) consisted of the total number of apnea or hypopneas per hour of sleep. An AHI of 1 or less was considered to be normal, while an AHI of 1-5 was defined as mildly increased, 5-10 moderately increased and >10 severely increased. All PSG studies were evaluated by two sleep medicine clinicians.

The Centers for Disease Control and Prevention (CDC) recommendations relevant for sleep practices during COVID-19 were followed at our department. AASM also advises sleep clinicians to follow the recommendations of the CDC [12]. According to the measures taken, telehealth strategies in terms of assessing the COVID-19 risk were used to evaluate and triage patients before the day they were scheduled to be seen. Triage protocols were used to determine if an appointment was necessary or if the patient could be managed from home. The goal was to avoid unnecessary exposure and to protect both the health care workers and patients.

All patients and their companions were asked to come to the hospital wearing a medical face mask and performing hand sanitization. At the entrance of the hospital children were permitted entry to our department with one parent only. Temperature checks were done at the entrance of the outpatient clinic. Decals or colored tape on the floor were placed 6 feet apart to show the patients where to stand. A questionnaire was prepared and risk factors and symptoms related to COVID-19 were questioned in another isolated room before going into the examination room. All patients and their companions were asked whether they came in close contact with any COVID-19 patient or had symptoms compatible with COVID-19. All patients underwent SARS-CoV-2 polymerase chain reaction (PCR) testing prior to sleep studies. Because of the possibility of false-negative PCR test results, sleep studies of the patients with symptoms suggestive of COVID-19 were delayed for at least one month.

Moreover, the staff was provided with all the appropriate personal protective equipment including surgical gown, gloves, medical face masks and for aerosol generating procedures N95 respirators (or the equivalent).

In our sleep laboratory, the recordings are performed with video-monitoring in order to allow the technician to examine the patient from a separate room and intervene only when strictly necessary. During the pandemic, rooms were cleaned according to the guidance for disinfection and ventilated with fresh air before admitting new patients.

Ethical approval was obtained from the ethics committee of our university (Reference number: GO 21/501).

Statistical Analyses

The SPSS V.22.0 (IBM Corp., Armonk, NY, USA) software was used for statistical analyses. All continuous variables were non-normally distributed and analyzed using Mann-Whitney U test and expressed as median (interquartile range-IQR). Categorical variables were presented as percentages (%) and analyzed using Chi-square test (with or without continuity correction) or Fisher's exact test. A value of $p<0.05$ was considered statistically significant.

RESULTS

Evaluation of the numbers of patients and diagnostic procedures

A total of 10068 patients were seen at our pediatric pulmonology department and 311 sleep studies (3%) were performed during the pre-pandemic period in 2019. The median age of the patients who

underwent sleep studies in 2019 was 7 (2.5-11.5) years (164 male, 147 female). Ninety-nine (31.8%) PAP titration studies were performed of which 46 were CPAP and 53 were BPAP. The remaining 212 (68.2%) PSGs were performed for diagnostic purposes.

A total of 5666 patients were seen at our outpatient department and 211 patients (3.7%) underwent sleep studies during the COVID-19 pandemic in 2020. The median age of the patients who underwent sleep studies in 2020 was 9 (4-12) years (127 male, 84 female). Compared to the previous year prior to the pandemic, although there was a slight decrease in the number of sleep studies (n=211 in 2020 vs. 311 in 2019), the frequency has increased from 3% to 3.7% (211 tests/5666 total number of outpatient visits in 2020 vs. 311/10068 in 2019). Of the 211 sleep studies conducted in 2020, 46 (21.8%) were PAP titration studies, including 8 CPAP and 38 BPAP. Compared to the pre-pandemic period, a decrease in the frequency of total PAP studies from 31.8% to 21.8% was observed.

By the end of 2020, with the necessary precautions taken, no increased risk of COVID-19 was detected in any of our patients undergoing sleep studies or the healthcare staff assisting the procedure. Additional to all the taken measures, every patient without exception underwent SARS-CoV-2 PCR testing prior to the sleep study and COVID-19 was not detected in any of our patients. Patients were additionally questioned for symptoms of COVID-19, around 2 weeks after their sleep study when they contacted us to learn of their results, none of the participants were found to have any complaints compatible with COVID-19. According to the evaluation in the outpatient clinic or via telephone, the sleep studies of 18 patients with symptoms such as fever, cough, dyspnea, muscle pain, sore throat, headache, chest pain that was compatible with COVID-19 were postponed and home isolation was recommended.

Evaluation of the indications of the sleep tests

Polysomnography

In 2019, of the 212 patients that underwent PSG, 24% (n=51) had Down syndrome, 7.5% (n=16) had Prader-Willi syndrome, 6.6% (n=14) had mucopolysaccharidosis, 6.1% (n=13) had obesity, 5.1% (n=11) had spinal muscular atrophy, 4.7% (n=10) had Duchenne muscular dystrophy and 2.8% (n=6) had epilepsy. The remaining 91 PSGs were done for rare conditions (e.g., ROHHAD syndrome, Bardet-Biedl syndrome, Joubert syndrome, myotonic dystrophy, etc.).

In 2020, of the 165 patients that underwent PSG 11.5% (n=19) of patients had Down syndrome, 10.9% (n=18) had spinal muscular atrophy, 7.8% (n=13) had epilepsy, 6.6% (n=11) had Prader-Willi syndrome and 3.6% (n=6) had mucopolysaccharidosis. The remaining 98 PSGs were done for other indications (e.g., Canavan disease, Pompe disease, Krabbe disease, etc.).

In 2020, compared with 2019, the number of PSGs decreased by 22.1%, from 212 to 165 (Figure 1). The largest group tested were patients with Down syndrome both before and during the pandemic.

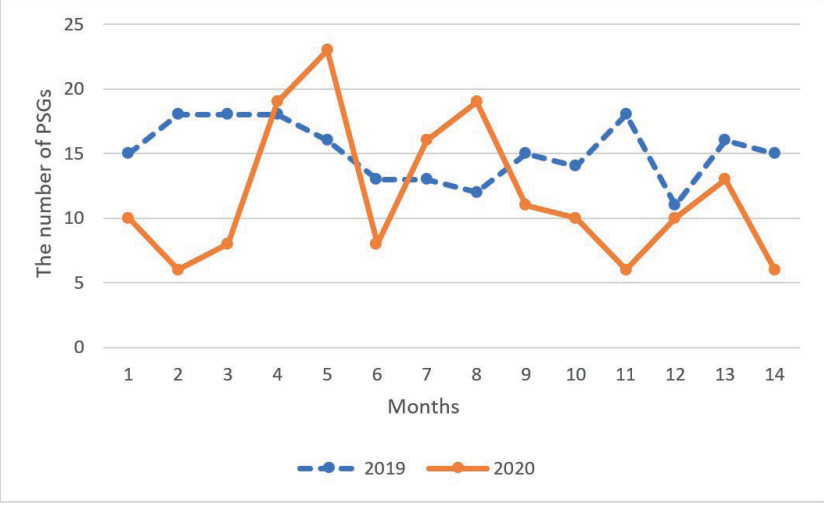

Figure 1. The number of PSGs by month

The number of PSGs by month in 2019 were more stable while serious fluctuations were seen in the number of PSGs in 2020 due to closures and reopenings.

PAP titration studies

In 2019, 99 PAP titration studies were performed. Twenty two percent (n=10) of patients with Down syndrome, 13% (n=6) with Prader-Willi syndrome and 8.6% (n=4) with obesity underwent CPAP titration studies while 19.5% (n=9) patients with Prader-Willi syndrome and 7.5% (n=4) with Down syndrome underwent BPAP titration studies. The remaining PAP titration studies were done for different indications (e.g., Jeune syndrome, Rubinstein-Taybi syndrome, Crouzon syndrome, pontine glioma, etc.).

In 2020, we performed a total of 46 PAP titration studies. Down syndrome was the most common indication and was performed on 10 patients. Fifty percent (n=4) of the patients with Down syndrome underwent CPAP titration while 15.7% (n=6) with Down syndrome and 10.5% (n=4) with spinal muscular atrophy underwent BPAP titration studies. The remaining PAP titration studies were done due to other indications (e.g., infantile neuroaxonal dystrophy, Smith-Lemli-Opitz syndrome, arthrogryposis multiplex congenita, etc.)

In 2020, compared with 2019, the number of PAP titration studies decreased by 53.5%, from 99 to 46 (Figure 2). The largest group tested were patients with Down syndrome both before and during the pandemic.

Evaluation of the PSG results

Results of 377 PSGs performed both in 2019 and 2020 were analyzed. Unavailable data from 34 patients and 12 PSG results with a sleep efficiency of 30% or less were not included in the analysis. The data presented here are from 331 PSGs, of which 191 were performed in 2019 and 140 in 2020.

Of the PSGs performed in 2019, 29.3% (n=56) was determined as mild apnea, 18.3% (n=35) as moderate apnea and 32.5% (n=62) as severe apnea. The median AHI score was found as 5 (1.7-14.7) events per hour. Sleep apnea was not detected in 38 (19.9%) patients.

Of the PSGs performed in 2020, 45.7% (n=64) was determined as mild apnea, 11.5% (n=16) as moderate apnea and 19.3% (n=27) as severe apnea. The median AHI score was 2.5 (1.1-7.7) events per hour. Thirty-three (23.5%) patients did not have sleep apnea in 2020.

The median AHI score in 2019 was higher compared to 2020 (AHI score 5 vs 2.5/hour; p=0.001, respectively).

DISCUSSION

PSG is an essential tool for the diagnosis and treatment management of several sleep disorders. The COVID-19 pandemic has had massive effects on healthcare procedures, including sleep medicine. Early in the course of the outbreak, sleep laboratories abruptly shut down in accordance with social distancing measures. As medical facilities prepared to reopen, taking into consideration the rate of infection in the community and the urgency of the sleep study, it was necessary to reschedule sleep medicine practices during the pandemic

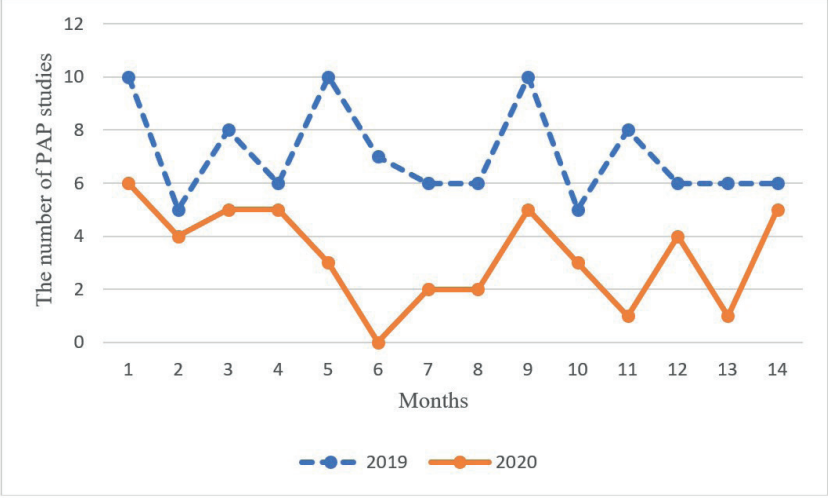

Figure 2. The number PAP studies by month

The number of PAP studies by month in 2020 was markedly declined compared to 2019.

[13]. Here we describe the effects of the COVID-19 pandemic on our sleep laboratory practices and provide our experience to conduct sleep studies safely. There are few studies about the impact of the pandemic on sleep medicine and the individual measures taken by the centers in order to prevent viral spread.

COVID-19 most commonly spreads via respiratory droplets during close contact. The transmission also occurs by airborne inhalation or through contact with contaminated surfaces. Airborne transmission of SARS-CoV-2 can occur during medical procedures that generate aerosols [14]. These procedures are more likely to generate higher concentrations of infectious respiratory aerosols than coughing, sneezing, talking, or breathing. Open suctioning of airways, sputum induction, cardiopulmonary resuscitation, endotracheal intubation and extubation, NIV (e.g., BPAP, CPAP), bronchoscopy, manual ventilation are considered aerosol-generating procedures [15]. On the other hand, we have little knowledge on whether PAP titration as a part of the sleep study emits the same amount of aerosol as NIV. In a study, CPAP therapy with different masks was evaluated and a well-fitted oronasal mask was found to be safe with a negligible dispersion of aerosol [16].

AASM recommendations concerning sleep practices during COVID-19 were updated repeatedly, most recently on January 2021 [17]. According to these recommendations, PAP titration and split night studies were postponed due to the potential for aerosolization, except in emergencies. Similarly, while some centers suggested stopping PAP titration studies, others did not agree with this interruption [18]. In accordance with the recommendations, we did not perform PAP titration studies unless there was a strict necessity and the frequency of PAP titration studies decreased in our sleep practices during the pandemic. We generally performed PAP titration studies for the first time in patients in whom we decided to start PAP therapy. However, we preferred not to do repetitive PAP titration studies if not strictly necessary for the patients who were under PAP treatment. In addition, in certain situations where we had to perform the sleep studies, all of our staff followed disinfection rules and used appropriate personal protective equipment.

While certain measures such as the restriction of socializing and non-urgent hospital admissions, closure of schools and the installation a curfew caused a decrement in hospital admissions, patients especially those with chronic diseases and their parents were also hesitant to visit hospitals [19]. In a recent study, a decline in the numbers of outpatient clinic visits and pediatric pulmonology procedures were observed due to the pandemic [20]. However, PSG and PAP titration therapy are indispensable studies for certain indications. In some cases, not performing a PAP titration, in particular, can lead to unacceptable health risks. For this reason, the continuity of these tests should be ensured by making decisions in accordance with the indications and taking the necessary precautions.

AASM also recommended that visits be conducted via telemedicine [13]. Several studies have found telehealth services to be both effective and helpful in other fields of pediatric pulmonology [21]. Our study also showed that the risk of transmission of COVID-19 to health care providers or other patients was preventable with the appropriate precautions. Although the total number of sleep studies did decrease during the pandemic compared to the previous year prior to the pandemic, the frequency did increase from 3% to 3.7%. To date, none of our healthcare staff including our sleep technicians have been infected with SARS-CoV-2.

In our study, before the pandemic the largest group of patients to undergo sleep studies were patients with Down syndrome and indications of sleep studies during the pandemic did not change. PSG helps diagnose obstructive sleep apnea (OSA) in patients with Down syndrome and since there is also a need for pressure support in most patients with OSA, PAP titration studies are commonly used to determine the pressure needed.

Multiple randomized trials have demonstrated that a home-based diagnostic and treatment strategy is as effective as a lab-based strategy for most patients [22]. The AASM guidance also advises the use of home sleep apnea testing (HSAT) in certain conditions during the ongoing pandemic. HSAT may be considered as an alternative for the diagnosis of OSA, although the current gold standard in children is in-lab PSG. HSAT is potentially more cost effective, convenient, and accessible. However, the

current evidence on the feasibility and diagnostic accuracy for pediatric OSA is limited. Furthermore, HSAT is not indicated for the diagnosis of other sleep-related breathing disorders.

Although there was a slight decrease in the number of sleep studies in 2020 compared to 2019, the increase in the frequency could be attributed to the decrease in outpatient clinic visits owing to the pandemic. During this period, there was a significant decrease in PAP titration studies, while a relative increase in the number of PSGs was observed. This result may suggest that the PSGs of the patients who needed a faster evaluation were prioritized due to the pandemic. However, when the PSG results were examined, the median AHI scores were found to be lower in 2020 compared to 2019. One of the reasons may be that the number of sleep studies performed on patients with chronic diseases (e.g., Down syndrome, neuromuscular disorders, mucopolysaccharidosis) has declined, as can be seen in patients with chronic lung diseases due to the anxiety about applying to a hospital during the pandemic [19]. Another reason could be that patients exaggerated their symptoms due to COVID-19 related anxiety or the fact that pre-evaluation to determine the indication was less optimal. The serious fluctuation in the number of monthly visits in 2020 due to closures and reopenings also strengthens this final interpretation. However, because of the descriptive design of this study, we could not establish a cause-effect relationship.

Our study has several limitations. First of all, the design of the study is not adequate to determine whether the number of hospital applications decreased only due to the COVID-19 pandemic. Secondly, we could not compare the results of our study with another one, because to date this is the first study about the effects of the COVID-19 pandemic on sleep laboratory practices. Additionally, the prognosis of patients whose PAP titration studies and PSGs were postponed is unknown. Whether the diagnostic power of sleep studies performed during the pandemic has decreased due to the implementation of measures is also unknown. Furthermore, when applying the results of this study to clinical practice, sleep centers themselves should take into account the fluctuations in the rate of infection.

In conclusion, our study showed that the pandemic has had negative effects on sleep medicine practices. However, after deciding to perform sleep studies within the risk-benefit balance, they can be done safely with the appropriate infection control measures. Due to the possibility that the pandemic may prolong, to decrease its unfavorable effects and aggrievedness on our patients it is necessary to manage sleep laboratory practices with urgency rather than postponing them.

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Author contribution

Study conception and design: BS, NE, UÖ; data collection: BS, BO, DAT, HNB, and IG; analysis and interpretation of results: BS and NE; draft manuscript preparation: EY, DD and NK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Hacettepe University (Protocol no. GO 21/501/2021).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Exploring the distribution and prognostic effect of the ABO blood types of COVID-19 patients during delta and omicron waves: A case control study

Hakan Göker[1]
ORCID: 0000-0002-1039-7756

Olgu Erkin Çınar[1]
ORCID: 0000-0003-1226-5797

Rashad Ismayilov[2]
ORCID: 0000-0002-7093-2722

Ela Özdemir[2]
ORCID: 0000-0003-2735-918X

Ümit Yavuz Malkan[1]
ORCID: 0000-0001-5444-4895

Elifcan Aladağ Karakulak[1]
ORCID: 0000-0002-1206-9908

Yahya Büyükaşık[1]
ORCID: 0000-0002-2700-295X

Nilgün Sayınalp[1]
ORCID: 0000-0002-5748-4056

İbrahim C. Haznedaroğlu[1]
ORCID: 0000-0001-8028-9462

Osman Özcebe[1]
ORCID: 0000-0002-0359-5148

Gülçin Telli Dizman[3]
ORCID: 0000-0001-8195-3345

Meliha Çağla Sönmezer[3]
ORCID: 0000-0001-6529-5282

Ahmet Çağkan İnkaya[3]
ORCID: 0000-0001-7943-8715

Haluk Demiroğlu[1]
ORCID: 0000-0002-6790-8748

[1] Department of Hematology, Hacettepe University Faculty of Medicine, Ankara, Türkiye.

[2] Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Türkiye.

[3] Department of Infectious Diseases and Clinical Microbiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye.

Corresponding Author: Hakan Göker
E-mail: hgoker1@yahoo.com

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ABSTRACT

Objective: We aimed to delineate the effects of the ABO groups and the main clinical outcomes with the current SARS-CoV-2 variants, i.e., delta and omicron.

Materials and Methods: In this retrospective case-control study, the total 360 adult COVID-19 patients who were followed in the pandemic waves of delta and omicron variants and had ABO blood group analysis were included and divided into two groups according to the waves of variant. Demographic characteristics, comorbidities, length of hospitalization and intensive care needs, survival and ABO groups of cases were recorded. These groups were then compared with the ABO group distribution of population-reflecting 1881 healthy individuals and 186 historical alpha variant cases.

Results: The demographic characteristics of the case groups and control group were similar. ABO distributions of the delta and omicron wave groups compared to the control group did not show a statistically significant difference. While advanced age ($p<0.001$) and presence of comorbidity ($p=0.006$) showed statistically significant differences in terms of overall survival, ABO blood group was not found to be a risk factor for mortality ($p=0.114$ in delta, and 0.526 in omicron), hospitalization time ($p=0.148$ in delta, $p=0.224$ in omicron), and intensive care unit admission ($p=0.096$ in delta, $p=0.229$ in omicron).

Conclusion: The risk of infection among ABO blood groups, which has been shown in previous studies for the alpha variant against group A and in favor of group O, does not appear to be valid for delta and omicron period patients. Therefore, the anti-infective measures, especially vaccination, should not differ for individuals according to ABO blood group.

Keywords: COVID-19, blood groups, delta variant, omicron variant.

INTRODUCTION

Many million people have died from coronavirus disease-19 (COVID-19), out of approximately 430 million cases, and thousands of deaths continue worldwide [1]. The COVID-19 causes a wide spectrum disease ranging from asymptomatic contagious to fatal respiratory failure, and it cannot be predicted with high accuracy which patient will have a poorer prognosis. Factors and biomarkers that may predict the course of the disease are still an area of research, although a long period has passed since the onset of the pandemic. In this context, many factors including demographics such as gender and ethnicity, comorbidities, routine tests such as blood glucose and vitamin D, inflammatory biomarkers such as IL-6 and TNF-alpha, have been evaluated in studies [2-6]. Since the discovery of blood groups at the beginning of the 20th century, interest in the role of blood groups in infectious diseases has continued [7]. Today, it is possible to find publications on the relationship of all kinds of pathogens, including bacteria, fungi, parasites, and viruses, with dozens of different blood group systems [8]. Among viruses, the relationship of influenza with blood groups has been investigated for decades [9]. The relationship between coronaviruses, including SARS-CoV subtypes and blood groups, has been demonstrated in various studies [10, 11].

Along with the pandemic caused by SARS-CoV-2, the relationship with the ABO blood groups was investigated. In a previous study, we found that the risk of infection may be increased in group A and the risk may be less in group O [12]. However, many different variants have caused consecutive pandemic waves to date, and the present study is designed to investigate whether the previously determined relationship with blood groups is also valid in new variants including delta and omicron. This study aims to delineate the effects of the ABO groups and the main clinical outcomes with the current SARS-CoV-2 variants, i.e., delta and omicron.

PATIENTS AND METHODS

Inclusion, Exclusion Criteria, and Patient Groups

Adult patients (>18 years old) who applied to Hacettepe University Hospitals between 1 May 2021 - 1 February 2022 were diagnosed with COVID-19, and whose SARS-CoV-2 variant was assumpted as delta or omicron were included in this retrospective cohort. Cases without ABO group analysis were excluded. As a result, the medical records of 4,600 patients were examined and, 360 cases were analyzed as the study group. Then, the cases in the study group were divided into two groups; delta wave and omicron wave patients. The basic demographic data of the patients, the follow-up setting (outpatient or inpatient), duration of stay, and intensive care unit admission, and whether the infection resulted in death were recorded.

In order to compare the patients' distribution among blood groups with the population at risk, 1881 healthy individuals, who applied to the Hacettepe University Blood Bank between 1 March 2020 and 1 May 2020, were included as the control group. The blood group distributions, age, and sex of these patients were recorded. Finally, the blood group distributions of the patients were compared with our study in the early alpha variant period of the pandemic [12] as a historical control group and the differences from the previous 186 COVID-19 patients were analyzed. Ethics committee approval for this study was obtained from the Hacettepe University Non-interventional Clinical Researches Ethics Board. Approval was also obtained from the General Directorate of Health Services of the Ministry of Health of the Republic of Turkey.

Variant Assumption of SARS-CoV-2 Positive Clinical Samples

The COVID-19 infection was diagnosed with SARS-CoV-2 polymerase chain reaction (PCR) positivity with a maximum of thirty cycle threshold (CT) value made from nasopharyngeal swabs as the universal standard.

Since variant analysis could not be performed from all samples in our center, the pandemic wave after May 2021, which WHO declared "variant of concern (VOC)", was taken as a basis for the delta variant period [13]. In this context, patients diagnosed between 1 May 2021 and 1 November 2021 were recorded as delta variant wave patients. Similarly, all cases after 1 December 2021 were recorded as omicron wave patients.

Statistical Analyses

Analyses were made using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The descriptive statistics were presented as frequency (percent), mean ± standard deviation (SD), or median (min-max). The χ2 test was used to compare the proportions in different categorical groups. Continuous variables were investigated with visual and analytical methods to determine the normal distribution and analyzed with the Mann-Whitney U test or the Student`s t-test. Odds ratios and their significance were determined by univariate logistic regression analysis. The Kaplan-Meier survival estimates were calculated. The log-rank test was used to identify the independent effects on survival. Risk factors for mortality were specified by Cox regression analysis. A 5% type-I error level was used to infer statistical significance.

RESULTS

In the total 360 delta (n=185) and omicron (n=175) wave COVID-19 patients, the mean age was 44.8±17 years. The number of female and male patients was similar (52.2% vs. 47.8% respectively, p=0.399). Fifty (13.9%) patients were 65 years of age or older. The mean age of the alpha group (historical control) was 44.5±16.8 years, the delta group was 46.7±17.3 years, and the omicron group was 42.8±16.9 years (p=0.097). The frequency of female sex in the alpha, delta, and omicron groups was 46.2%, 51.4%, and 53.1%, respectively (p=0.392).

The O blood group percentage was 24.7% in the alpha, 34.1% in the delta, 37.7% in the omicron groups, and 37.2% in the healthy controls (p=0.007). Post-hoc analyses revealed a statistically significant difference between the alpha group and controls (p=0.001) for O blood type. While there was no statistically significant difference between the delta and omicron groups with the controls, they showed significant differences from the alpha group (p=0.049 and 0.001, respectively). The frequency of A blood type was 57% in the alpha group, 43.7% in the delta group, 40% in the omicron group, and 38% in the controls (p<0.001). As the statistical difference was due to the alpha group (v. the controls, p<0.001), there was no statistically significant difference between the delta, omicron groups, and the controls. Therewithal, the statistical difference between alpha with delta and omicron was also significant (p=0.011 and 0.003, respectively). According to B and AB blood types, the groups showed similar distributions (Table 1).

The median follow-up period of the patients was 26 days (1 - 245). While there was no statistically significant difference in overall survival (OS) by gender (p=0.868), the OS of the ≥65 years was lower than those below (3.8 vs. 7.8 months, p<0.001, Figure 1). When alpha, delta and omicron variants were compared, no statistically significant difference in OS was observed (2.6, 7.4, and 2.9 months, respectively, p=0.164). The presence of comorbidity was a significant predictor of mortality (HR: 146, 95% CI: 4.3-4955, p=0.006, Figure 2). Moreover, there was a negative correlation between the number of comorbidities and OS (Figure 3). There was no statistically significant relationship between ABO blood groups with mortality in delta and omicron patients (p=0.114 and 0.526, resp.). Similarly, no significant difference was detected between the ABO blood groups in terms of hospitalization time (p=0.148 in delta, p=0.224 in omicron) and intensive care unit admission (p=0.096 in delta, p=0.229 in omicron) in patients infected with new variants.

Table 1. The demographics and the blood types according to the groups

Characteristics	Alpha, n (%)	Delta, n (%)	Omicron, n (%)	Controls, n (%)	*p* value
Age, mean±SD, y	44.5±16.8	46.7±17.3	42.8±16.9	-	0.097
Female sex	86 (46.2%)	95 (51.4%)	93 (53.1%)	-	0.392
Blood types					
0	46 (24.7%)[a]	63 (34.1%)[b]	66 (37.7%)[b]	701 (37.2%)[b]	**0.007***
A	106 (57%)[a]	81 (43.7%)[b]	70 (40%)[b]	716 (38%)[b]	**<0.001***
B	20 (10.8%)	29 (15.7%)	18 (10.3%)	277 (14.7%)	0.190
AB	14 (7.5%)	12 (6.5%)	21 (12%)	188 (10%)	0.219

*Post-hoc analysis showed a statistical significance between the a`s and b`s in the respective rows.

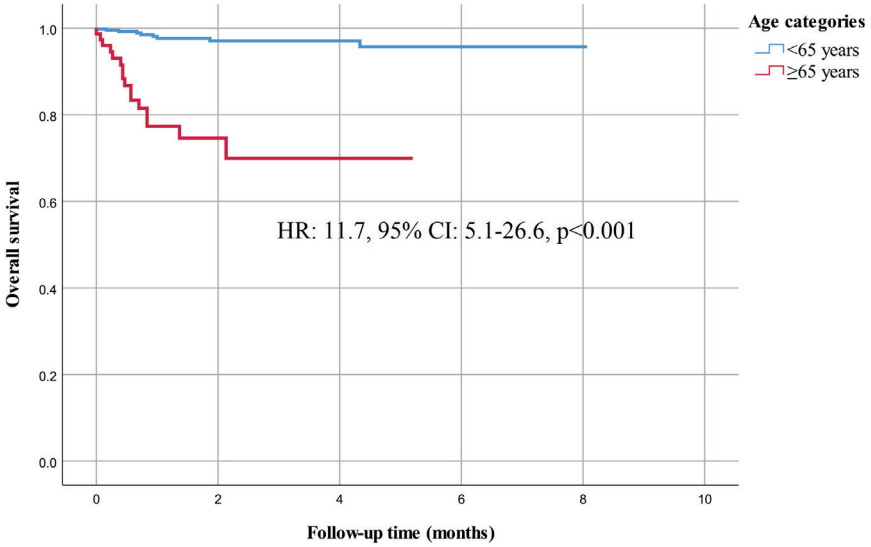

Figure 1. The age categories and overall survival

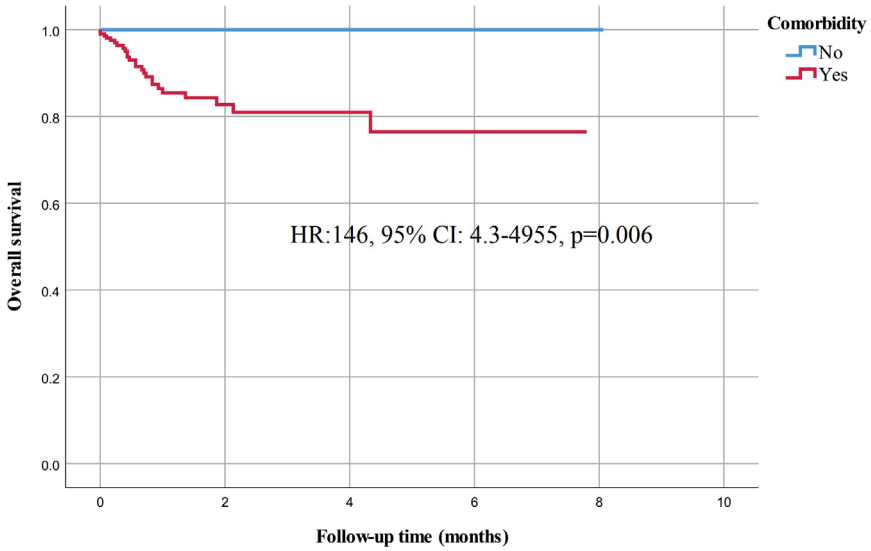

Figure 2. The comorbidity and overall survival

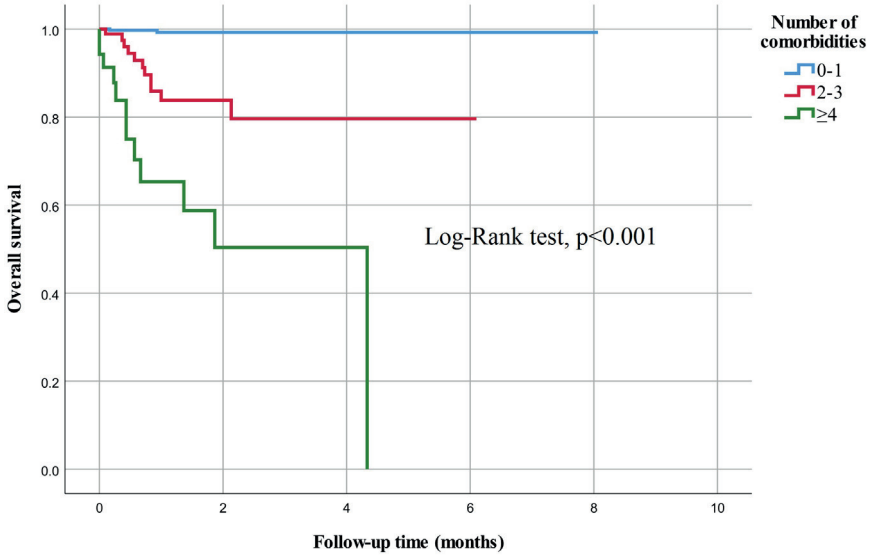

Figure 3. Number of comorbidities and overall survival

DISCUSSION

Like other common viruses, the relationship between coronaviruses and blood groups has been studied for a long time. SARS-CoV-2 enters the cell by providing viral adhesion with its spike protein (S), which has more than 20 potential N-glycosylation sites [11]. The fact that the S protein contains structures similar to ABO antigens may lead to a change in the risk of infection in individuals with antibodies to these antigens. However, it has been hypothesized that secretory status and anti-ABO antibody titers also affect the risk of infection. Studies show that even the country's development level can be effective in the antibody titers in the population [14]. In the 2003 major SARS outbreak in Hong-Kong, analysis of 45 health staff with similar blood group distributions to population showed that blood type was associated with the risk of infection [10]. Group O participants were less likely to become infected when compared with non-O participants (OR: 0.18; 95% CI: 0.04-0.81). For this reason, only qualitative ABO group analysis will not be able to give precise information about infection risk, and the findings cannot be extrapolated to all populations. The studies that each country will conduct on its own population will be more valuable about blood groups and infections.

In the Turkish population, studies examining this risk were conducted [15-17]. The joint results found in these studies; people with group A are more likely to be infected, but the blood group does not have a significant effect on the course of the diseaseexcept for the study of Sertbas et al., which showed that the risk of intubation increased in the AB group [16]. It is seen in this study that the risk in group A, which we also confirmed before, is not valid for the period in which the current waves with delta and omicron variants. This difference can be hypothesized that the new variants contain lesser A-antigen-like structures than the alpha.

On the other hand, the low infection risk of group O, shown in many studies in the literature, was also confirmed in the Turkish population by Yanardag et al. in a study of 823 people [18]. Similarly, although the risk of infection with the alpha variant decreased in group O, this protection seems to have disappeared in the delta and omicron dominant pandemic waves, according to the present study findings.

The most important limitation of this study is that it includes patient groups that can be considered somewhat small for the pandemic period with a high incidence of COVID-19.

In conclusion, apart from ABO group antigens, there are many individual blood group factors, such as antibody titers, and it is impossible to determine all of them for each individual. In cases of outbreaks where antigenic changes are common, such as viral pandemics, cross-sectional results cannot be generalized to the whole period. Nevertheless, these results provide evidence that anti-infective approaches such as using masks, social distancing, hygiene, and especially vaccination should not change for the ABO blood groups.

Author contribution

Study conception and design: HG, OEÇ, and RI; data collection: RI, EÖ, and ÜYM; analysis and interpretation of results: HG, OEÇ, RI, EAK, YB, NS, İCH, OÖ, and GTD; draft manuscript preparation: RI, OEÇ, MÇS, AÇİ and HD. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

This study was approved by the Hacettepe University Non-interventional Clinical Researches Ethics Board (Project no: GO 22/180; Decision no: 2022/03-44; Date: 15.02.2022). Approval was also obtained from the General Directorate of Health Services of the Ministry of Health of the Republic of Turkey.

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Determination of the glycemic index values of the Turkey-specific ice cream

Nuket Yumuk[1]
ORCID: 0000-0001-9692-0044

Çağlar Keskin[2]
ORCID: 0000-0001-5503-4468

Özgür Demir[2]
ORCID: 0000-0003-1398-9009

Mustafa Şahin[2]
ORCID: 0000-0002-4718-0083

Adile Begüm Bahçecioğlu Mutlu[2]
ORCID: 0000-0003-0777-8934

Şule Canlar[2]
ORCID: 0000-0001-7695-9611

Rıfat Emral[2]
ORCID: 0000-0002-5732-2284

Murat Faik Erdoğan[2]
ORCID: 0000-0002-0867-6393

Sevim Güllü[2]
ORCID: 0000-0002-0955-0717

Vedia Tonyukuk Gedik[2]
ORCID: 0000-0003-0685-2020

Nilgün Başkal[2]
ORCID: 0000-0001-9157-4816

Demet Çorapçıoğlu[2]
ORCID: 0000-0003-0940-9147

[1]Ankara University, School of Medicine, Department of Nutrition and Dietetics, Ankara, Turkey.

[2]Ankara University, School of Medicine, Department of Endocrinology and Metabolic Diseases, Ankara, Turkey.

Corresponding Author: Çağlar Keskin
Ankara University, School of Medicine, Department of Endocrinology and Metabolic Diseases, Ankara, Turkey.
E-mail: caglaron@hotmail.com

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ABSTRACT

Objective: The glycemic index (GI) is defined as the effect of consumed food on blood glucose relative to the reference food. The aim of this study is to determine the GI value of "Atatürk Orman Çiftliği (AOÇ)" ice cream, which is unique to our country.

Method: This study included 18 adult healthy individuals with normal body mass index (BMI) values (18.5-24.9 kg/m^2) (Female/Male: 10/8). Individuals participating in the study were invited to the our outpatient clinic on different days for two weeks to consume 2 test foods (AOC ice cream) and 2 reference foods (glucose) after 12 hours of fasting. Venous blood samples were taken at 0, 15, 30, 45, 60, 90 and 120 minutes after consumption of reference and test foods and glucose values were recorded. The glycemic index value of the test food was calculated by multiplying by 100 the ratio of the sum of the area under the curve obtained from the test food to the sum of the area under the curve obtained from the reference food.

Results: The median values of the area under the curve of the reference food and the test food were 2360.88 (483.75-4132.5) and 475.95 (44.88-1980), respectively ($p<0.001$). The Glycemic index value of the test foods was 21.46 (4.08-409.3) according to the reference food.

Conclusion: In this study, the glycemic index value of the Turkey-specific "Atatürk Orman Çiftliği" ice cream was found to be 21,46 (4.08-409.3) (Low). These types of foods with a low glycemic index may be preferred to increase the dietary compatibility of the patient with type 2 diabetes, especially at snack meals.

Keywords: carbohydrates, glycemic index, glycemic load, ice-cream.

INTRODUCTION

Canadian researchers Jenkins and his colleagues first mentioned the term glycemic index (GI) in 1981 [1]. It was originally developed for diabetic patients, but it has also been found to be a viable method for healthy individuals. GI is defined basically as a ranking of foods based on the postprandial blood glucose response compared with a reference food [2,3]. The World Health Organization (WHO) and the United Nations Food and Agriculture Organization (FAO) have reported that carbohydrates should be classified according to their glycemic index [3]. According to this classification, food is divided into three groups as low (GI <55), medium (GI: 55-70) and high (GI> 70) GI foods. Foods with low GI raise blood glucose slowly, while foods with high GI elevate blood glucose rapidly.

Calculation of the glycemic index of foods requires a series of tests. The standards for the calculation of the GI and the details are stated in FAO's "Carbohydrates in Human Nutrition" report. Glycemic load (GL) a different terminology refers to how much the amount of carbohydrates in the portion of the food can affect blood sugar. GL is a measure that combines both the quality and the quantity of consumed carbohydrates [4]. It is calculated by multiplying the amount of carbohydrate in the serving portion of the food with the GI of the food. Foods with a GL ≤10 are classified as low GL, and those with a value ≥20 as high GL.

In recent years it has been shown that feeding with low glycemic index foods provides a delay in the development of type 2 DM, and provides better glycemic regulation and better metabolic control in type 2 DM patients [5,6]. Therefore it is important to calculate the glycemic index values of all foods consumed in daily life and to make an optimal nutrition plan suitable for each individual. Unfortunately, the studies on determining the glycemic index of foods are rather limited in our country. 'Atatürk Forest Farm ice cream' (AOC ice cream) is a nutrient consumed frequently in our country. The aim of this study is to determine the GI value of the country-specific AOC ice cream.

METHOD

Subject Selection: After signing a consent to adhere to the experiment, 18 healthy adult volunteers (8 male and 10 female) without endocrinological or metabolic disease were included in the study. After recording the anthropometric measurements of the participants (body weight, height, body mass index, waist circumference) they were assessed metabolically by an endocrine specialist before the study. Fasting blood glucose, fasting insulin, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, VLDL cholesterol, thyroid stimulating hormone, alanine transaminase, aspartate transaminase, total protein, albumin, creatinine levels and total blood counts were measured from blood samples taken after 10-12 hours fasting from individuals.

Blood Sampling and Analysis: In the first phase of the study, the sample of AOC ice cream was sent to The Scientific and Technological Research Council of Turkey Marmara Research Center (TUBITAK Marmara Research Center) to analyze the measures of moisture, fat, protein, nutrient fiber and ash content and the amount of AOC ice cream containing 50 g digestible carbohydrate (Table 1). In the second phase of the study, the individuals consumed the test nutrient (AOC ice cream) for 2 times and the reference nutrient (glucose) for 2 times after 12 hours fasting on different days at one week intervals. The day before the test, they were asked not to make changes in their diet, not to use alcohol, not to consume caffeine-containing beverages, to limit the consumption of carbohydrate foods, to sleep as well as possible and to have normal (similar) physical activity. The prepared foods were measured with a 0.01 gauge scale and the amounts consumed by the individuals were adjusted. They consumed of the food containing 50 g digestible

Table 1. Analysis results showing the contents of the test food

Energy	178 kcal/100 g
Moisture	64.43 g/100 g
Ash	1.51 g/100 g
Protein	6.95 g/100 g
Carbohydrate	18.66 g/100 g
Fibre	<0.65 g/100 g
Fat	8.54 g/100 g
Calcium	216mg/100 g

carbohydrates within 10 minutes (venous blood samples were taken from individuals before consuming the reference and test food). During the measurements, individuals are required to be stable in terms of physical activity. Venous blood samples were taken at 15, 30, 45, 60, 90, and 120 th minutes from all participants after consumption of reference and test foods, and glucose values were recorded. Blood glucose values were marked on the graphic of averages of the two measured values thus blood glucose curves of the reference food and the test food were obtained. Then, by plotting a horizontal line from the blood glucose value at the 0 th minute (starting point), only the area above the line (the remaining area under the curve) is accounted for. The glycemic index value of the test food was calculated by proportioning the area under the curve obtained from the test food to the area under the curve obtained from the reference food and multiplying by 100. This study was approved by Ethics Committee of Ankara University School of Medicine (date: 27.06.2016, number: 12-553-16). Informed consent was obtained from all individual participants included in the study.

Statistical Analysis: Continuous data were expressed as means ± standart deviations or medians and range. The percentage values were given in discrete data. The Mann-Whitney U test was used to compare two groups of continuous variables. The Wilcoxon Test was used to compare the individual area under the curve (AUC) values of glucose and AUC values of AOC ice cream.

RESULTS

Eighteen healthy subjects were included in the study (Female/ Male: 10/8). The mean age, height, weight, BMI and waist circumference values of the individuals were respectively 29.94 ± 8.15, 167 ± 0.11 cm, 63.35 ± 13.04 kg, 22.55 ± 2.18 kg/m^2, 76.17 ± 9.29 cm. No pathological value was found in the biochemical parameters of the individuals (Table 2). The median values of the area under the curve produced by the reference food and test food consumed by the individuals are 2360.88 (483.75-4132.5) and 475.95 (44.88-1980), respectively (p <0.001) (Table 3). The GI value of the test food was 21.46 (4.08-409.3) according to the reference food. Also, the glycemic load was calculated as 4 for the test food AOC ice cream (GL greater than 20 is considered high, a GL of 11–19 is considered medium, and a GL of 10 or less is considered low). There was no difference between gender in terms of GI value of the ice cream (p=0.173) (Table 4).

Table 2. Baseline characteristics of individuals

	Male (n=8)	Female (n=10)	p value
Age (years)	28 (21-43)	27 (22-43)	0.829
Height (cm)	176 (168-196)	160 (147-167)	<0.001
Weight (kg)	77 (59-94)	53.45 (49-62)	<0.001
Body Mass Index(kg/m^2)	24.6 (20.6-24.8)	21.5 (19.09-24.48)	0.006
Waist circumference (cm)	85.5 (78-90)	67.5 (62-78)	<0.001
Fasting Blood Glucose (mg/dl)	91 (86-100)	86 (83-100)	0.101
Insulin (µIU/ml)	6.7 (4.2-10.1)	6.25 (4-13.2)	0.829
Total Cholesterol (mg/dl)	175 (136-198)	170.5 (143-196)	0.829
LDL (mg/dl)	111 (82-129)	92 (82-129)	0.274
HDL (mg/dl)	43.5 (32-58)	60.5 (47-76)	0.001
Triglyceride (mg/dl)	97.5 (47-150)	76.5(57-136)	0.203
TSH (mIU/ml)	2.06 (0.55-3.46)	2.14(0.77-3.74)	0.762

Table 3. Area under the curve (AUC) of test food and reference food

	Median (min-max)	p
AUC of Glucose	2360.88 (483.75-4132.5)	<0.001
AUC of Ice cream	475.95 (44.88-1980)	
GI of test food	21.46±(4.08-409.3)	

Table 4. Glycemic index values of ice cream in different genders

	Male	Female	
	Median (min-max)	Median (min-max)	p
GI	27.9±(12.4-409.3)	19.9(4.08-88.1)	0.173

DISCUSSION

According to the classification of the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO), foods are divided into three groups according to their GI values (>70 high, 55-70 moderate, <55 low). In this study, the glycemic index value of the Turkey-specific 'Ataturk Forest Farm ice cream' (AOC ice cream) was found to be 21,4 (4.08-409.3). This value is much lower than the average value determined for ice cream in the international glycemic index table (51±3) [7].

Generally, at least 10 healthy volunteers are required for glycemic index determination studies [8]. In order to increase the statistical significance, we included 18 individuals in this study. Although it is known that gender is not an important factor in the glycemic index calculations we took care to ensure that the number of male and female participants in this study was balanced as much as possible [9].

Thomas and colleagues found that the standard deviations were significantly higher in the glycemic index determination methods with shorter tests and less frequent blood sampling [10]. Therefore we used the glycemic index calculation method proposed by the Food and Agriculture Organization for non-diabetic individuals. Thus seven blood samples were collected over 2 hours to calculate incremental AUC.

Carbohydrates are the main energy source for humans and carbohydrate metabolism plays a significant role in several diseases. High glycemic index meals cause rapidly rising blood glucose and insulin levels. Many studies have shown that low glycemic index diets improve insulin resistance, beta cell damage, endothelial damage and dyslipidemia [11-13]. As a result of a meta-analysis, diabetic individuals who consume lower GI foods were reported to have better blood glucose control and a significant decrease in HbA1c levels [4]. The results of epidemiologic studies indicate the relationship between high GI or GL diets and increased myocardial infarction [14,15]. In another study it was reported that a high GI diet increased the risk of metabolic syndrome by 41% compared to a low GI diet [16]. It has been also shown in previous studies that low glycemic index foods increase insulin sensitivity in patients with type 2 diabetes and reduce daily insulin requirements in patients with type 1 diabetes, and reduces serum triacylglycerol levels [4,12,17]. Unfortunately, in our country studies on determining glycemic index are very limited. There are a few studies of glycemic index determination made with different types of bread and honey consumed in our country [18]. It is the first study to determine the glycemic index for Turkey-specific ice cream.

There are several factors that may affect the GI of a food, including the presence of other macronutrients, protein, fat and moisture contents, carbohydrate structures, differences in processing, preparation and cooking methods and acidity. It is argued that both the amount and source of carbohydrates are important determinants of postprandial glucose and insulin response in studies [19]. Therefore the same food may have a different glycemic index value even with the same amount of carbohydrates. The presence of large amounts of protein and fat may reduce the glycemic response by increasing insulin secretion and slowing gastric emptying. Compared to ice cream produced in Switzerland the fat and protein content was significantly higher in Turkey-specific ice cream (carbohydrate, protein, fat and calorie content of Switzerland specific ice cream per 100 grams are 13.2 gr, 1.8 gr, 7.4 gr, 128 kcal, respectively). We think that the protein and fat content of the test food (AOC ice cream) has an important role in obtaining this result. Furthermore, cooling process may have played a role in these results. Although the effect of cooling on the glycemic index is not clear, it can be speculated that it may decrease the glycemic index values by increasing the resistant starch ratio [20,21].

There are a limited number of studies in the literature aiming to determine the glycemic index of ice cream. Although the average glycemic index of ice cream is accepted as 51±3 in the international glycemic index table, the glycemic index values range from 36 to 68 depending on the fat content of the ice cream. In a study of Buker at all, the glycemic load of a cholesterol-free tofu-based frozen dessert (TFD) and ice cream was compared. They found that sucrose and lactose-rich ice cream caused less glycemic load than TFD-containing glucose-rich carbohydrates [22]. In another study conducted by Ganon et al, when 50 gr glucose was ingested as milk, ice cream or only glucose; glycemic response and glycemic load were found to be highest in the glucose alone group. Following the ingestion of 50 gr carbohydrate as ice cream, they found that the

plasma glucose response was higher than for milk ingestion [23]. In our study, similar results were obtained with the test food that has lactose-rich content.

It is generally accepted that the glycemic index is a property of foods and that it is not affected by the characteristics of individuals such as age, sex, body mass index and ethnicity [24]. In contrast to this view, it has been shown in some studies that demographic variations of individuals can change the mean glycemic index values of foods. For example, Venn et al. showed that ethnicity has a significant effect on the mean glycemic index values in a study of 73 healthy Whites and 27 healthy Asians individuals [25]. We think that ethnic differences in the study population may play a role in the low glycemic index value of the product used in our study.

Showing glycemic index values on food labels is a current issue all over the World, especially in countries such as Australia and Canada. The Canadian Ministry of Health has published a report on the idea that GI values should be included in nutritional labeling and that this information will help consumers make healthier choices. In order to discuss these issues in our country, it is necessary to determine the glycemic index of frequently used food [26]. In the future, more prospective studies are required to assess the relationship between a lower glycemic index diet and the development of chronic diseases including diabetes, cardiovascular diseases and cancer. Also, glycemic index studies with different products in diabetic or prediabetic patients are needed.

In conclusion, the present study has provided reliable values of GI and GL for food commonly consumed in Turkey. The GI value of AOC ice cream was 21.46 (4.08-409.3). In addition, the glycemic load (GL) of 100 gr AOC ice cream was calculated as 4 (low). As it is thought that about half of the daily needed energy is derived from carbohydrates the consumption of carbohydrates with a healthy and low glycemic index is an important issue. AOC ice cream is consumed frequently in our country. These types of foods with a low glycemic index may be preferred to increase the dietary compatibility of the patient, especially at snack meals.

Author contribution

Study conception and design: NY, DÇ, NB, SG, MFE, VTG, ÖD, MŞ, and RE; data collection: NY, ÇK, and ŞC; analysis and interpretation of results: NY, MŞ, and ÇK; draft manuscript preparation: NY, ÇK, and ABB. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ethics Committee of Ankara University School of Medicine (Protocol no. 12-553-16/27.06.2016).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

The prognostic significance of serum lactate dehydrogenase to albumin ratio in pancreatic ductal adenocarcinoma

Hüseyin Bilge[1]
ORCID: 0000-0001-7203-2288

Ömer Başol[1]
ORCID: 0000-0001-9237-4648

Baran Demir[2]
ORCID: 0000-0002-1416-8520

Abdullah Oğuz[2]
ORCID: 0000-0002-8711-8110

1 SBU Gazi Yaşargil Training and Research Hospital, Department of General Surgery, Diyarbakır, Türkiye.

2 Dicle University Faculty of Medicine, Department of General Surgery, Diyarbakır, Türkiye.

Corresponding Author: Hüseyin Bilge
E-mail: dr.huseyinbilge@hotmail.com

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ABSTRACT

Objective: This study was performed to investigate the prognostic role of lactate dehydrogenase/albumin ratio (LAR) and pancreatic ductal adenocarcinoma (PDAC) with initial curable resection treatment.

Materials and Methods: This retrospective study was conducted with the data of patients with resectable PDAC. The (ROC) analysis showed that the optimal sill value for pretreatment LAR was 91.43 and this threshold value was used in other analyses. Univariate and multivariate analyses were performed to determine the prognostic factors for overall survival (OS).

Results: Our study consisted of 70 patients with a mean age of 59.5±13.2 years and 37 (52,9%) women. OS was 50 months in LAR <91.43 (n = 32) patients and 27,7 months in LAR≥91.43 (n=38) patients, respectively. Kaplan–Meier curves showed that LAR≥91.43 was significantly associated with worse OS (p=0.029). Multivariate analyses proved that LAR was an independent predictor in resectable PDAC patients (p=0.017).

Conclusion: Our results showed that a high pre-treatment LAR level was a unfavorable prognosticator in PDAC patients undergoing curative resection. LAR has the potential to be a prognostic biomarker in clinical practice.

Keywords: pancreas ductal adenocarcinoma, lactic dehydrogenase, albumin, LAR, survival.

INTRODUCTION

Pancreatic cancer, one of the deadly cancers, is a fatal disease due to its late diagnosis and lack of treatment protocols. It is the fourth most important reason for cancer-depended deaths. One-year survival of pancreatic cancer patients is less than 10% [1, 2]. Surgery is still the best choice for treatment. Only 20% of the patients are diagnosed in the early stages and other patients are diagnosed in the late stages. Therefore, surgery becomes difficult and ineffective. Curative resection can be performed in only 10-15% of patients [3]. Chemotherapy is used only to improve the quality of life in patients who are not suitable for surgery. Successful surgical resection has been shown to be one of the leading factors in the treatment [4]. For this reason, there is a need for new strategies to help the early diagnosis, prevention, effective treatment and prognosis prediction of the disease.

The glycolytic activity increases under adequate oxygen supply in cancer cells and this is defined as the "Warburg Effect" [5]. Warburg Effect is considered as one of the majör factors in the initiation, progression and invasion of pancreatic cancer [6]. At the end of glycolysis, lactate dehydrogenase (LDH) takes place as a catalyzer for converting pyruvate to lactate. LDH measurements (assays) are cheap and easy analyses that are frequently used in daily practice. LDH levels may

reflect the size, growth and invasive potential of the tumor.

LDH level has been found to be an important prognostic marker in pancreatic cancers and other gastrointestinal malignancies [7–12]. LDH gene expression is increased in many malignant tumors such as esophagus [13], stomach [14], lung [15], colorectal [16] and pancreas [17]. Serum albumin is closely related to malnutrition and is one of the good indicators of regular nutritional status. The changes in serum albumin are associated with the progression of many diseases, as is the loss of tumor-induced albumin in the inflammatory response. Thus, it may be a valuable prognostic factor for poor survival in pancreatic cancers. In published studies, low serum albumin levels were found to be associated with poor prognosis in cancers of the esophagus, stomach, colorectal and pancreas (18-20). There are limited studies evaluating the effect of LDH/albumin ratio (LAR) on prognosis in cancer patients. An increase in the LAR rate has been associated with worse prognosis in hepatocellular and esophageal cancer [21,22].

To the best of our knowledge, there is no study investigating the effect of LAR on prognosis in pancreatic ductal adenocarcinoma (PDAC). In this study, we aimed to evaluate the relationship between preoperative LDH/Albumin ratio and overall survival (OS) in PDAC patients who underwent curable resection.

METHODS

Study population and ethics statement

Seventy pancreatic ductal adenocarcinoma patients who underwent curable resection in General Surgery Clinic in January 2012 and December 2019 were included in our study. The study was approved by the Ethics Committee of our University for clinical and pathological data (7/5/20-151). Informed consent was obtained from all participants.

The Inclusion criteria are;

1) Laboratory parameters including LDH and albumin values measured at the time of diagnosis or in the past month, 2) Surgical resection as R0, 3) Complete clinical and pathological features and follow-up data 4) no neoadjuvant chemotherapy.

The exclusion criteria are;

1) Cancer treatment history, 2) Inflammatory disease, 3) Systemic disease, 4) Hemolysis blood, 5) R0 resection not possible, 6) Distant organ and liver metastases, 7) Early mortality in hospital, 8) Having secondary cancer

Data collection

Key clinical features like gender, age, serum LDH levels, albumin, carcinoembryonic antigen, carbohydrate antigen 19-9, tumor location, differentiation, and TNM stage were collected by medical records. Routine laboratory measurements (including white blood cells, neutrophils, lymphocytes, and platelet counts) were performed prior to treatment. It was correlated with laboratory values and excluded in the presence of hemolysis. Tumor staging was processed with respect to the UICC-AJCC TNM Classification System (23). Clinical, laboratory and pathological features were categorized while making comparisons between groups.

Follow-up

OS was defined as the time interval from surgery to date of death. The last follow-up throughput for patients without any incident symptoms composed the terminal record.

Cutoff determination of LAR

LAR cut-off values were found as 91.43 for optimal calculation (ROC analysis- Figure 1). It resulted in sensitivity of 67.6% and a specificity of 60.6% (p=0.019, Table 1). This cut-off was used in other analyses. Accordingly, there were 32 (32/70, 45.7%) patients with a pre-treatment LAR value below 91.43, and 38 (38/70, 54.3%) patients above 91.43.

Table 1. ROC Analysis (Death situation)

	Cut-off Value	Sensitivity (%)	Specificity (%)	Area(%)	P-value
LDH/Albumin	91,43	67,6	60,6	66,3	0,019

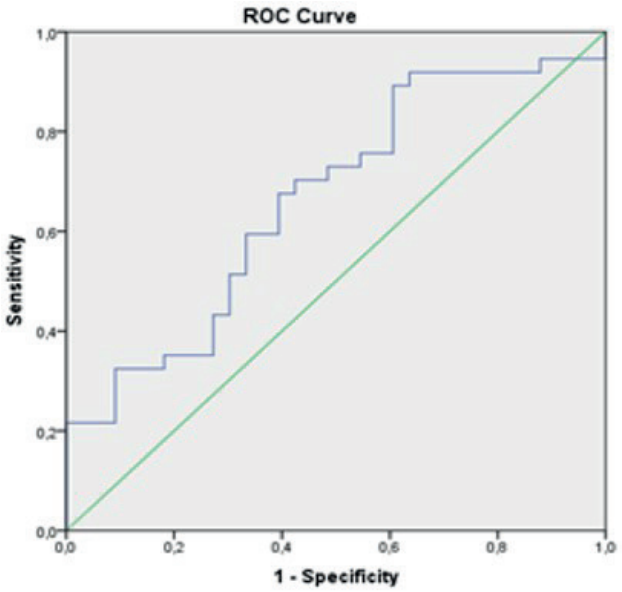

Figure 1. The determination of the best cut-off of pretreatment LDH-to-albumin ratio. The cutoff value was 91. 43

Statistical analysis

Constant variables were defined as means with standard deviations (SD) and ranged medians. Categorical variables were shown as percent frequency. Chi-square test, Fisher's exact test (categorical variables) and independent sample t-test (continuous variables) were used to compare differences between sub-groups. Overall survival was calculated by the Kaplan-Meier method. A log-rank test was used to compare the results. The Cox regression model was used to examine independent prognostic risk factors. The p <0.05 value was considered statistically significant. Data were analyzed with SPSS® Statistics 22 version.

RESULTS

In our study, 37 (52.9%) of the patients were female and 33 (47.1%) were male. The mean age of the patients was 59.5 ± 13.2 years. The demographic and clinical characteristics of the patients are summarized in Table 2.

The median pursuit time was 24.57 months (2-80). Patients with a follow-up shorter than 2 months and with mortality were excluded from the study.

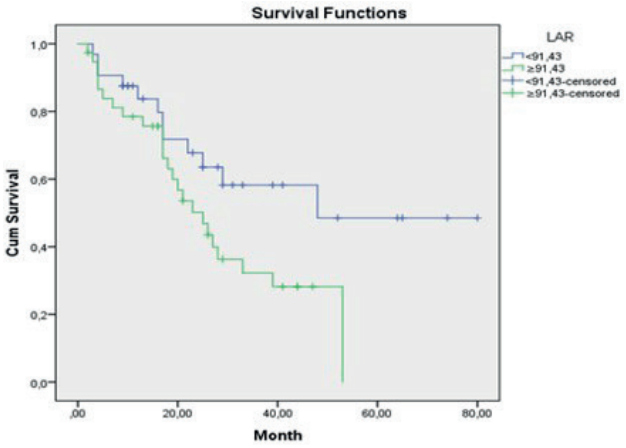

Figure 2. Kaplan- Meier Overall survival of patients
(Abbreviations: LAR, lactic dehydrogenase to albumin ratio)

The mean disease-free survival was 17.60 months (interquartile range, 2-80 months).

According to Kaplan Meier's analysis results, overall survival of patients was 50 months in patients with LAR <91.43 and 27.7 months in patients with LAR≥91.43. Kaplan–Meier curves showed that LAR≥91.43 was significiantly associated with bad OS (p<0.029) (Table 3 and Figure 2).

Patients were evaluated in two groups as <91.43 (n=32) or ≥91.43 (n=38) according to LAR value. High CEA≥ 5 ng/ml (p<0.001), CA 19-9 ≥ 37 ng/ml (p=0.019), low albumin level (p<0.001), lymph node positivity (p=0.002) and advanced tumor stage (p=0.001) p<0.001) was found to be significant in favor of the high LAR group.

In the comparison between the two groups; high CEA≥ 5 ng/ml (p<0.001), CA 19-9 ≥ 37 ng/ml (p=0.019), low albumin level (p<0.001), lymph node positivity (p=0.002) and advanced tumor stage (p<0.001) significant in favor of high LAR group.

Univariate analysis was performed to determine the prognostic value of the LAR level and other clinical variables for OS (Table 4). Age ≥65, LAR≥91.43, CA 19-9 ≥37 ng/ml, CEA ≥5 ng/ml, lymph node positivity (N2), lymphovascular and perineural invasion were associated with survival. In the multivariate analysis, only LAR ≥91.43 and age ≥65 were associated with overall survival (Table 5).

Table 2. The relationship between LDH-to-albumin ratio and clinicopathological parameters in the present cohort

Variable	Total	LAR<91.43 n, (%)	LAR≥91.43 n, (%)	P-value
Patients	70(100)	32(45.7)	38(44.3)	
Age				0.642
<65	45 (64.3)	22 (68.8)	23 (60.5)	
≥65	25 (35.7)	10 (31.3)	15 (39.5)	
Sex				0.842
Female	37(52.9)	16 (50.0)	21 (55.3)	
Male	33(47.1)	16 (50.0)	17 (44.7)	
ASA PS classification				0.732
1-2	28 (40.0)	14 (43.8)	14 (36.8)	
3-4	42 (60.0)	18 (56.3)	24 (63.2)	
Tumor location				0.290
Head	66 (94.3)	29 (90.6)	37 (97.4)	
Corpus	2 (2.9)	1 (3.1)	1 (2.6)	
Tail	2 (2.9)	2 (6.3)	0 (0.0)	
T catagory				0.387
1-2	40 (57.1)	16 (50.0)	24 (63.2)	
3-4	30 (42.9)	16 (50.0)	14 (36.8)	
Lymph node status				0.612
pN0	45 (64.3)	19 (59.4)	26 (68.4)	
pN1	20 (28.6)	11 (34.4)	9 (23.7)	
pN2	5 (7.1)	2 (6.3)	3 (7.9)	
TNM stage				0.328
1	27 (38.6)	10 (31.3)	17 (44.7)	
2	37 (52.9)	20(62.5)	17 (44.7)	
3	6 (8.6)	2 (6.3)	4 (10.5)	
Preoperatif LDH (U/L)	253.3±86.1	199.0±37.8	299.0±89.0	<0.001
Preoperatif Albumin (gr/dl)	2.76±0.71	3.26±0.63	2.35±0.46	<0.001
Preopreratif LDH/Albumin	99.9±46.7	63.3±16.4	130.6±41.4	<0.001
Anjuvant Therapy	42 (60.0)	21 (65.6)	21 (55.3)	0.378
Recurrence	39 (55.7)	16 (50.0)	23 (60.5)	0.521

Abbreviations: LAR, lactic dehydrogenase to albumin ratio; LDH, lactic dehydrogenase; ASA, American Society of Anesthesiologists; PS, physical status

Table 3. Test of equality of survival distributions for the different levels of LAR

Overall Comparisons			
	Chi-Square	*df*	*Sig.*
Log Rank (Mantel-Cox)	4,766	1	**,029**

DISCUSSION

The prognosis of pancreatic cancer is related to various factors such as age, profession, history of disease, tumor location, surgical method, postoperative complication and TNM stage [24]. "Low albumin and high LDH levels are indicative of worse prognosis in most cancers" was the hypothesis of the study. This hypothesis was formed with the question of "what effects LAR will have on prognosis?".

We concluded that the LAR increase in PDAC patients with curative resection adversely affected survival. To the best of our knowledge, this was the first study to investigate the relationship of LAR with prognosis in PDAC. We think that the high LAR cut-off value in our study indicated the poor

Table 4. Univariate analyses of overall survival of patients

Variable	Univariate analysis OR (95% CI)	P-value
Age≥65	2.101-8.169	<0.001
ASA PS classification. ≥III	0.564-2.388	0.686
Need adjuvant therapy	0.404-1.521	0.471
Preoperatif LDH (U/L)	0.368-0.882	**0.012**
Preoperatif Albumin (gr/dl)	0.999-1.006	0.149
Preopreratif LDH/Albumin	1.001-1.012	**0.032**
LVI +	1.300-4.774	0.006
PNI+	1.860-7.188	<0.001
Recurrence	2.192-11.974	**<0.001**
CEA≥5	1.898-7.943	**<0.001**
CE19-9≥37	1.192-6.863	**0.019**
LAR≥91.43	1.051-4.216	0.036
PLR≥118.27	1.073-4.868	**0.032**
NLR≥2.95	1.404-5.603	**0.003**

Abbreviations: OR, odds ratio; LVİ, lymphovascular invasion; PNI, perineural invasion; LAR, lactic dehydrogenase to albumin ratio; CEA, Carcinoembryonic antigen; ASA, American Society of Anesthesiologists; PS, physical status; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Table 5. Multivariate analyses of overall survival of patients

Variable	β	Multivariate analysis OR (95% CI)	P-value
Age≥65	0.994	1.176-6.214	0.019
LVI +	0.079	0.323-3.604	0.902
PNI +	0.894	0.752-7.947	0.137
CEA≥5	0.777	0.964-4.906	0.61
CA19-9≥37	0.515	0.667-4.206	0.273
LAR≥91.43	0.918	1.181-5.315	0.017

Abbreviations: β, beta; OR, odds ratio; LVI, lymphovascular invasion; PNI, perineural invasion; LAR, lactic dehydrogenase to albumin ratio; CEA, Carcinoembryonic antigen.

prognosis of PDAC. The effect of LAR on prognosis should undoubtedly be supported by prospective studies with large patient groups. However, its easy application and low cost may increase the use of LAR as a marker in many cancer types.

In the presence or absence of oxygen, oxidoreductase LDH converts pyruvate to lactate. It plays an important role in the metabolism of cancer cells. LDH-A is overexpressed in hypoxic carcinomas and metastatic cancer cells. The levels of them are correlated with tumor viability. Serum LDH levels are an indirect marker of tumor hypoxia, angiogenesis, and poor prognosis in many tumor types (9–11,18–23,25–28). LDH elevation is also associated with the intensity of tumor angiogenesis, tumor volume and tumor progression [29]. In this sense, LDH levels may partially reflect tumor volume. Rong et al. found that LDH directly supported the growth of pancreatic cancer cells [17].

Serum albumin level is an important marker of malnutrition. Recent studies showed that albumin was a systemic factor that reflects both nutritional and chronic inflammatory conditions. Hence, fallen albumin value is also a poor prognostic factor in PDAC patients. However, albumin is still a controversial marker for prognosis [30]. LDH and albumin are both routine tests in clinical application. This makes them practical. Also, hypoalbuminemia especially increases the risk of deep vein thrombosis, enterocutaneous fistula and surgical site infection. As a result, it significantly increases the term of hospital remain and complication incidence [7].

There are very limited and current studies on the prognostic impact of LAR. Feng at al. included 346 patients with esophageal SCC in their study. They concluded that LAR was effective on survival. In this study, the cutoff rate of LAR was determined as 5.5 and it was deterrmined that LDH and albumin

alone did not have any effect on prognosis [21]. In our study, we determined that LDH and albumin values did not affect prognosis alone. In another study, Gan at al. [22] concluded that a high LAR level in hepatocellular cancer was associated with a bad prognosis.

Small number of patients, retrospective design and long-term follow-up to confirm results were the main limitations of our study. The optimal cut-off rate for preoperative LAR was unbeknown. However, 91.43 was determined as the cut-off rate using the outcomes of a ROC analysis, which was linked to the poor prognosis of PDAC patients likely to be high.

CONCLUCION

High LAR value is an unfavorable prognosticator for OS in PDAC patients undergone curative resection. Our results are retrospective, but should be supported by prospective, large patient groups and long follow studies. However, LAR may be a candidate parameter for clinical use in predicting cancer mortality and morbidity.

Author contribution

Study conception and design: HB, AO and ÖB; data collection: HB and BD; analysis and interpretation of results: HB and AO; draft manuscript preparation: Hb, AO and ÖB. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Dicle University Faculty of Medicine Ethics Commitee (protocol no: 151/7.5.2020)

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

High 30-day readmission rates in hospitalized patients with heart failure: Strengthening the need for a multidisciplinary and integrated approach

Hatice Bolek[1]
ORCID: 0000-0001-8659-7327

Sila Cetik[1]
ORCID: 0000-0002-5038-0553

Furkan Ceylan[1]
ORCID: 0000-0002-1944-0861

Ertugrul Cagri Bolek[2]
ORCID: 0000-0003-3886-2813

Oguz Abdullah Uyaroglu[1]
ORCID: 0000-0003-0440-2026

Mine Durusu Tanriover[1]
ORCID: 0000-0001-9565-4389

[1] Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Türkiye.

[2] Division of Rheumatology, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Türkiye.

Corresponding Author: Hatice Bolek
E-mail: hati.kocc@gamil.com

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ABSTRACT

Background: Heart failure (HF) is a common disease which is one of the most common causes of hospitalization. Although mortality rates are decreasing, readmission rates are still quite high.

Objectives: We aimed to investigate the risk factors for readmission and death in patients who were hospitalized due to HF.

Design and Setting: Retrospective study, Hacettepe University, Ankara, Turkey

Methods: Patients hospitalized between 1 January 2014 to 31 December 2018 with the primary diagnosis of HF were included. Outcome variables were risk factors for 30-day all- caused readmission, 30-day HF related readmission, mortality.

Results: All-cause 30-day readmission rate was 34.8% and HF-related 30-day readmission rate was 21.2%. The factors associated with increased all-caused 30-day readmission were male gender, hyperlipidemia, chronic liver disease, malignancy. The factors associated with increased HF-related 30-day readmission were hyperlipidemia, chronic liver disease, inflammatory rheumatologic diseases, malignancy. Use of ACE-i was found to be protective against all-cause and HF-related 30-day readmission. Factors associated with mortality were ejection fraction <30%, chronic liver disease, acute kidney injury, hypoalbuminemia at the time of admission.

Conclusions: Nearly one third of patients in this cohort who were hospitalized with a primary diagnosis of HF were readmitted in the following 30 days. Having certain chronic diseases and conditions were associated with an increased risk for readmission and mortality. These findings point out to the special needs of HF patients, who require a proactive, integrated and multidisciplinary management strategy to control the risk factors and to improve the inpatient and transitional stages in the hospital.

Keywords: heart failure, hospital readmission, mortality, transitional care.

INTRODUCTION

Heart failure (HF) is a common clinical condition which affects millions of people worldwide with increasing numbers of new diagnoses each year [1]. It is a chronic, complex disease greatly despairing the quality of life of the patients, having psychological, social and financial impact on the families and putting a huge burden on the healthcare systems. Heart failure is one of the most common causes of hospitalization both in Europe and in the United States [2]. One million hospitalization due to heart failure annually was estimated and the number is expected to increase significantly [3]. Unfortunately, 2%-17% of patients who are admitted to hospital because of HF die in the hospital in that particular episode [4]. While mortality decreased with new treatments over the years, there was no change in the rate of hospitalization [5]. Although numbers are very different among studies, 20%-33% of patients hospitalized due to heart failure are readmitted to the hospital within the first 30 days after discharge and almost 70% are readmitted within one year [6-10]. Age, chronic obstructive pulmonary disease (COPD), liver diseases, diabetes mellitus (DM), peripheral vascular disease, stroke, renal dysfunction, malnutrition, hyponatremia, hypokalemia, anemia, high brain natriuretic peptide (BNP) levels, number HF hospitalization within one year were defined as risk factors for heart failure related readmission in previous studies [5,11-13]. On the other hand, the use of certain medications, such as angiotensin converting enzyme inhibitors (ACE-i), aldosterone receptors blockers (ARB), beta-blockers and sacubitril-valsartan in the treatment of HF not only reduce the mortality but also the readmission rates [11,14]. Twenty-seven percent of these readmissions can be prevented by optimization of medical care [15]. Identifying risk factors for readmission is crucial to define the interventions required and to provide the optimal care. Reducing hospital readmission rates increases the quality of health care and decreases the cost of hospitalization. In this study, we aimed to investigate the risk factors for 30 days readmission and mortality for HF in hospitalized adult patients in a tertiary care university hospital in Turkey.

METHODS

2.1. Patients and Protocol

This is a retrospective study that analyzes the hospitalization data of patients treated with the primary diagnosis of HF. Adult patients who were hospitalized in the internal medicine wards of a tertiary care university hospital between 1 January 2014 to 31 December 2018 due to HF were enrolled. Firstly; patients with relevant ICD-10 codes I50.0, I50.1, I50.2, I50.3, I50.4, I50.8, I50.9, I11.0, I13.0, I13.2, I25.0, I25.1 or the key word (heart failure) in the medical records were identified through the hospital information management system. Among these patients, those who have transthoracic echocardiography (TTE) with the reporting of the ejection fraction (EF) at the time of or before the admission were detected and screened. Patients who were admitted for the first time with the primary diagnosis of HF and whose ejection fraction was <50% on TTE were included in the study. Exclusion criteria were not having a HF-related diagnosis, having any hospitalization episode due to HF before 1 January 2014, not having a TTE before or at the time of that particular admission and having an EF of ≥50% on TTE.

Sociodemographic characteristic, comorbidities, laboratory findings and medical treatments were recorded for each episode, retrospectively.

This study complies with the principles of Declaration of Helsinki. This study has been approved by the University Ethics Commission (Approval number: GO 19/349).

End-points and Definitions

Since definitive causes of some patients' deaths were not known, the end point for survival analysis was determined as all-cause mortality until 31 December 2018. Since some patients died during hospitalization, only the variables at the admission were used in the mortality analysis. Second end-point was determined as 30-day readmission, which was defined as unplanned admission to the hospital within 30 days of discharge. Unplanned admission to the hospital with the primary

diagnosis of HF was accepted as HF-related 30-day readmission. Each hospitalization period was accepted as an episode and the episodes which end up with mortality were excluded from 30-day readmission analysis. Mortality analysis was done case based and readmission analysis was done episode based.

Hyperlipidemia was defined as a low-density lipoprotein (LDL) level above the target level according to European Society of Cardiology (ESC) 2019 Guidelines on dyslipidemias [16]. Overt hypo- or hyperthyroidism or usage of L- thyroxine or any antithyroid drug was considered as thyroid disease. Increase in serum creatinine by ≥ 0.3 mg/dl within 48 hours of hospital admission was accepted as acute kidney injury (AKI) [17]. Glomerular filtration rate < 60 ml/min/1.73 m^2 and history of renal transplantation were accepted as chronic renal disease. DM defined as use of any antidiabetic drug or meeting American Diabetes Association criteria for the diagnosis of diabetes [18]. Cirrhosis or any other liver dysfunction more than 6 months which caused by any pathology were considered as chronic liver disease. Other chronic diseases were recorded based on the medical records of the patients. Anemia was defined as hemoglobin (Hb) level of <13.0 g/dl for men and <12.0 g/ dl for women. Serum albumin level <3.5 g/dL was considered as hypoalbuminemia. Because no generally excepted cut-off level for brain natriuretic peptide (BNP) exists, BNP cut-off level which was used in Kaplan-Meier survival analysis was identified as 1000 pg/ mL by receiver operating curve (ROC) analysis with a positive predictive value of 66%, and negative predictive value of %53.

Statistical Analysis

All statistical analyses were done with IBM SPSS Statistics 24.0 statistical package program. Continuous variables were described as median (inter- quartile range, IQR) and categorical variables as percentages. Chi- square test was used to compare categorical variables and Mann–Whitney U test/Student's T-test/ Kruskal Wallis/ one-way ANOVA test were used to compare continuous variables. Logistic regression method was applied to calculate odds ratios (OR) to comprise the occurrence of event. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. Kaplan-Meier survival estimates were calculated. Possible factors identified with univariate analyses were further entered into the Cox regression analysis, with backward selection, to determine independent predictors of survival. P- values of <0.05 were considered as significant.

RESULTS

A total of 30228 patients were determined in the hospital information management system based on relevant ICD codes and "heart failure" key-word, and among them 2523 eligible patients were found to be hospitalized in Internal Medicine wards between 1 January 2014 to 31 December 2018 (Figure 1). Those who did not have TTE imaging before or at the time of admission, who were hospitalized with a primary diagnosis other than HF or who had previous hospitalization episodes due to HF before 1 January 2014 were excluded. Finally, 404 hospitalization episodes of 303 patients were included in the final analysis. One hundred ninety-one (36.9%) patients were male, median age was 72 (IQR=14) years and median EF was 35 (IQR = 18). The most common comorbidities accompanying HF were coronary artery disease (CAD) (74.9%), hypertension (HT) (67.7%) and hyperlipidemia (63%). Sociodemographic characteristics of patients are demonstrated in Table 1.

30-day readmissions

Since 63 out of 404 episodes ended with mortality, these episodes were not included in the readmission analysis and 339 hospitalization episodes were evaluated for 30-day readmission. All-cause 30-day readmission rate was 34.8% (118 episodes) and HF-related 30-day readmission rate was 21.2% (72 episodes). Atrial fibrillation (AF) (48.3%), hyperlipidemia (78.3%), thyroid dysfunction (22.2%), chronic liver disease (9.3%) and malignancy (26.3%) were more prevalent in patients who were hospitalized within 30-days compared to those patients who weren't. On the other hand, hyperlipidemia (80%), thyroid diseases (25%), chronic liver disease (9.7%), inflammatory rheumatologic diseases (18.1%) and malignancy (27.8%) were found to be more prevalent in patients who were admitted due to HF within 30-days of discharge compared to those who were

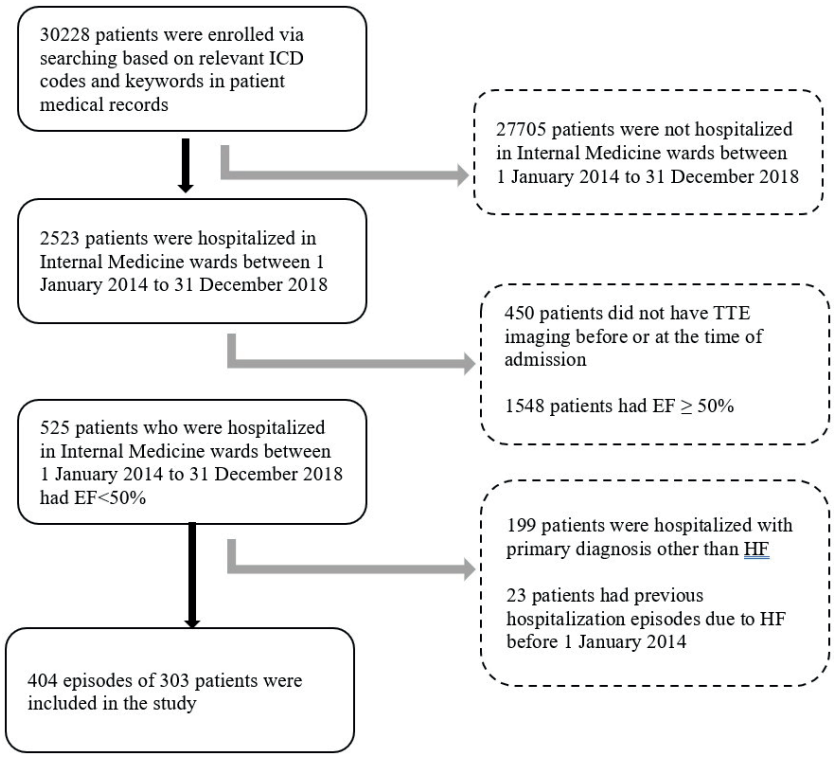

Figure 1. Study flow chart.

Abbreviations= HF= Heart failure, TTE= transthoracic echocardiography

Table 1. Baseline characteristics of patients.

		All patients (N=303)
Gender, Male		191 (63.7%)
Age, year (Median, IQR)		72 (14)
EF, % (Median, IQR)		35 (18)
EF range	EF <40%	178 (58.7%)
	EF 40-49%	125 (41.3%)
COPD		91 (30%)
DM		141 (46.5%)
AF		120 (39.6%)
CAD		227 (74.9%)
HT		205 (67.7%)
Chronic renal disease		154 (50.8%)
Hyperlipidemia		191 (63%)
Thyroid diseases		50 (16.5%)
PTE history		14 (4.6%)
Chronic liver disease		21 (6.9%)
Inflammatory rheumatologic diseases		28 (9.2%)
Malignancy[¥]		48 (15.8%)

Abbreviations: AF= Atrial fibrillation, COPD= Chronic obstructive pulmonary disease, CAD= Coronary artery disease, DM= Diabetes mellitus, EF= Ejection fraction, HT= Hypertension, IQR= Interquartile range, PTE = Pulmonary thromboembolism

[¥] Other malignancies than non-melanoma skin cancer

not re-hospitalized because of HF within 30 days (including patients either not re-hospitalized at all or hospitalized due to another reason except for HF). Median time for HF related readmission was 13.3 (IQR=15.5) days after discharge and the highest number of readmissions was on the 8th day after discharge. Patients who were re-admitted due to any cause or HF had lower rates of ACE-i use. General features of patients based on 30-day readmission were given in Table 2.

On multivariate analysis, factors determined to be independently associated with increased all-cause 30-day readmission rates included male gender (OR 1.816; 95% CI,1.022-3.226), hyperlipidemia (OR 2.845; 95% CI, 1.570-5.152), chronic liver disease (OR 4.717; 95% CI, 1.282-17.353) and malignancy (OR 1.988; 95% CI, 1.037-3.811) (Table 3a). Factors determined to be independently associated with increased HF-related 30-day readmission rates included hyperlipidemia (OR 2.771; 95% CI, 1.346-5.707), chronic liver disease (OR 6.496; 95% CI, 1.849-22.830), inflammatory rheumatologic diseases (OR 2.996; 95% CI, 1.263-7.110) and malignancy (OR 2.124; 95% CI, 1.041-4.332) (Table 3b). Use of ACE-i was found to be protective against both all-cause and HF-related 30-day readmission. Each 1 day increase in length of stay was associated with 4.6% decrease in HF-related 30-day readmission.

Table 2. Comparison of features of patients based on 30-day readmission.

		All episodes (N=339)	All-cause 30-day readmission (+) (N=118)	All-cause 30-day readmission (-) (N=221)	p	HF-related 30-day readmission (+) (N=72)	HF-related 30-day readmission (-) (N=267)	p
Gender, Male		209 (61.7%)	78 (66.1%)	131 (59.3%)	0.24	48 (66.7%)	161 (30.3%)	0.24
Age, year (Median, IQR)		73.50 (15)	74 (14)	72 (14)	0.20	74 (12)	72.50 (15)	0.55
EF, % (Median, IQR)		35 (15.5)	35 (15)	33 (17)	0.23	35 (13.7)	35 (17.5)	0.60
EF range	EF <40%	193 (56.9%)	69 (58.5%)	124 (56.1%)	0.67	45 (62.5%)	148 (55.4%)	0.28
	EF 40-49	146 (%43.1)	49 (41.5%)	97 (43.9%)		27 (37.5%)	119 (44.6%)	
COPD		106 (31.3%)	37 (31.4%)	69 (31.2%)	1	23(31.9%)	83 (31.1%)	0.89
DM		164 (48.4%)	**48 (40.7%)**	**116 (52.5%)**	0.04	31 (43.1%)	133 (49.8%)	0.35
AF		137 (40.4%)	**57 (48.3%)**	**80 (36.2%)**	0.03	32 (%44.4)	105 (39.3%)	0.50
CAD		259 (76.4%)	94 (79.7%)	165(74.7%)	0.35	58 (80.6%)	201(75.3%)	0.43
HT		253 (74.6%)	94 (79.7%)	159 (71.9%)	0.15	59 (81.9%)	194 (72.7%)	0.13
Chronic renal disease		189 (55.8%)	68 (57.6%)	121 (54.8%)	0.65	41(56.9%)	148 (55.4%)	0.89
Hyperlipidemia		228 (68.5%)	**90 (78.3%)**	**138 (63.3%)**	**0.006**	**57 (80.3%)**	**171 (65.3%)**	**0.02**
Thyroid diseases		56 (16.6%)	**26 (22.2%)**	**30 (13.6%)**	**0.04**	**18 (25%)**	**38 (14.3%)**	**0.04**
PTE history		15 (4.4%)	6 (5.1%)	9 (4.1%)	0.78	3(4.2%)	12 (4.5%)	0.90
Chronic liver disease		17 (5%)	**11 (9.3%)**	**6 (2.7%)**	**0.01**	**7 (9.7%)**	**10 (3.7%)**	**0.04**
Inflammatory rheumatologic diseases		36 (10.6%)	17 (14.4%)	19 (8.6%)	0.14	**13 (18.1%)**	**23 (8.6%)**	**0.03**
Malignancy		60 (17.7%)	**31 (26.3%)**	**29 (13.1%)**	**0.004**	**29 (27.8%)**	**40 (15%)**	**0.01**
AKI		144 (43.5%)	55 (47%)	89 (41.6%)	0.36	32 (45.1%)	112 (43.1%)	0.79
BNP admission, pg/mL (Median, IQR)		1517.50 (2011)	1422 (1473)	1544 (2442)	0.43	1422 (1433)	1544 (2168)	0.99
BNP discharge, pg/mL (Median, IQR)		732.5 (1266)	789.5 (810)	694.0 (1774)	0.23	880.5 (797)	657.5 (1541)	0.21
Hemoglobin admission, g/dl (Mean, SD)		11.32 (2.1)	10.97 (2.1)	11.5 (2.1)	0.78	10.18 (1.7)	11.59 (2.0)	0.45
Hemoglobin discharge, g/dl (Mean, SD)		10.93 (1.7)	10.62 (1.5)	11.09 (1.8)	0.22	10.16 (1.1)	11.11 (1.8)	0.26
Hematocrit admission, % (Mean, SD)		35.58 (6.4)	34.02 (6.4)	36.11 (6.3)	0.37	31.57 (5.5)	36.32 (6.3)	0.36
Hematocrit discharge, % (Mean, SD)		33.93 (5.1)	32.88 (4.6)	34.49 (5.2)	0.18	31.81 (3.6)	34.4 (5.2)	0.46
Creatinine admission, mg/dl (Median, IQR)		1.40 (1.1)	1.36 (0.9)	1.40 (1.2)	0.26	1.46 (0.8)	1.49 (1.1)	0.60
Creatinine discharge, mg/dl (Median, IQR)		1.27 (1.1)	1.29 (1.1)	1.27 (1.1)	0.97	1.33 (1.3)	1.26 (1.3)	0.62
Sodium admission, mEq/L (Median, IQR)		135 (6)	135 (5)	135 (7)	0.32	135 (6)	135 (6)	0.95
Sodium discharge, mEq/L (Median, IQR)		136 (5)	137 (5)	136 (5)	0.18	136 (5)	136 (5)	0.26
Albumin admission, g/dL (Mean, SD)		3.39 (0.7)	3.41 (0.7)	3.38 (0.6)	0.52	3.39 (0.8)	3.39 (0.8)	0.96
Albumin discharge, g/dL (Mean, SD)		3.20 (0.4)	3.17 (0.6)	3.25 (0.7)	0.13	3.16 (0.5)	3.24 (0.7)	0.26
Potassium admission, mEq/L (Median, IQR)		4.30 (0.9)	4.20 (0.8)	4.40 (1)	0.14	4.20 (0.8)	4.30 (1)	0.15
Potassium, discharge, mEq/L (Median, IQR)		4.30 (0.7)	**4.18 (0.7)**	**4.30 (0.9)**	**0.005**	4.18 (0.7)	4.32 (0.8)	0.06
IV diuretic treatment in the hospital		286 (85.4%)	101 (85.6%)	185 (85.3%)	1	63 (87.5%)	223 (84.8%)	0.71
Follow-on appointment at discharge		281 (83.9%)	101 (85.6%)	180 (82.9%)	0.64	62 (86.1%)	219 (83.3%)	0.72
Length of hospital stay, days (median, IQR)		13 (13)	13 (12)	14 (13.5)	0.54	**10 (10.25)**	**14 (13)**	**0.001**
Drugs prescribed at discharge								
Beta blocker		273 (83.7%)	98 (83.8%)	175 (83.7%)	1	63 (87.5%)	210 (82.7%)	0.37
ACE-i		78 (24.1%)	**18 (15.5%)**	**60 (28.8%)**	**0.007**	**8 (11.3%)**	**70 (27.7%)**	**0.004**
ARB		40 (12.3%)	16 (13.7%)	24 (11.5%)	0.60	13 (18.1%)	27 (10.6%)	0.10
MRA		124 (38.3%)	40 (34.5%)	84 (40.4%)	0.34	23 (32.4%)	101 (39.9%)	0.27
Digoxin		81 (25%)	30 (25.6%)	51 (24.6%)	0.89	17 (23.6%)	64 (25.4%)	0.88
Statin		153 (47.7%)	61 (53%)	92 (44.2%)	0.13	40 (57.1%)	113 (44.7%)	0.08

Abbreviations: ACE-i= Angiotensin converting enzyme inhibitors, AF= Atrial fibrillation, AKI = Acute kidney injury, ARB= Aldosterone receptor blockers, BNP= Brain natriuretic peptide, COPD= Chronic obstructive pulmonary disease, CAD= Coronary artery disease, DM= Diabetes mellitus, EF= Ejection fraction, HF= Heart failure, HT= Hypertension, IQR= Interquartile range, IV= Intravenous, MRA= Mineralocorticoid receptor antagonists, PTE = Pulmonary thromboembolism, SD= Standard deviation

Table 3. Independent predictors for 30-day readmission in multivariate logistic analysis.

3a. Independent predictors for all-cause 30-day readmission in multivariate logistic analysis.			3b. Independent predictors for HF-related 30-day readmission in multivariate logistic analysis.		
Variables	**Odds ratio (95% CI)**	**P-value**	**Variables**	**Odds ratio (95% CI)**	**P-value**
Gender, male	**1.816 (1.022-3.226)**	**0.042**	Gender, male	1.776 (0.898-3.512)	0.099
Age, year	1.021 (0.996-1.046)	0.100	Age, year	1.017 (0.987-1.048)	0.269
DM	0.755 (0.444-1.285)	0.300	**Hyperlipidemia**	**2.771 (1.346-5.707)**	**0.006**
AF	1.582 (0.938-2.667)	0.085	Thyroid diseases	2.072 (0.961-4.466)	0.063
Hyperlipidemia	**2.845 (1.570-5.152)**	**0.001**	**Chronic liver disease**	**6.496 (1.849-22.830)**	**0.004**
Thyroid diseases	1.696 (0.850-3.380)	0.134	**Inflammatory rheumatologic diseases**	**2.996 (1.263-7.110)**	**0.013**
Chronic liver disease	**4.717(1.282-17.353)**	**0.020**			
Malignancy	**1.988 (1.037-3.811)**	**0.039**	**Malignancy**	**2.124 (1.041-4.332)**	**0.038**
Serum potassium level	**0.587 (0.376-0.937)**	**0.025**	**ACE-i**	**0.331 (0.143-0.770)**	**0.010**
ACE-i	**0.480 (0.252-0.911)**	**0.025**	**Length of stay**	**0.954 (0.922-0.987)**	**0.007**

Mortality

Three hundred-three patients were included in the mortality analysis. Median follow-up time was 25 (IOR= 42.1) months. Kaplan-Meier analysis estimated that gender (p=0.021), EF range (p<0.001), chronic liver disease (p=0.002), AKI at the admission (p<0.001), serum BNP at the admission (p<0.001), hyponatremia at admission (p=0.048), hypoalbuminemia at admission (p<0.001) were risk factors for mortality. In addition to these variables; age, COPD, DM, AF, CAD, chronic renal disease, hyperlipidemia, thyroid dysfunction, inflammatory rheumatologic diseases, malignancy, anemia at admission were also evaluated in the Kaplan-Meier analysis, but no effect on mortality could be shown. Cox regression analysis model was constructed for the variables that were significant in the Kaplan-Meier analysis (Table-4). Factors associated with mortality in Cox regression analysis model were determined as EF<30% (OR 2.120; 95% CI, 0.431-3.088), chronic liver disease (OR 1.857; 95% CI,1.089-3.165), AKI (OR 1.584; 95% CI, 1.157-2.169) and hypoalbuminemia at admission (OR 1.576; 95% CI, 1.142-2.175). Kaplan-Meier analysis of these variables were given in Figure 2.

Table 4. Independent predictors for mortality in Cox regression analysis.

Variables	Odds ratio (95% CI)	P-value
EF 40-49% (reference)		
EF 30-39%	1.225 (0.804-1.867)	0.334
EF <30%	**2.102 (0.431-3.088)**	**<0.0001**
Chronic liver disease	**1.857 (1.089-3.165)**	**0.023**
AKI	**1.584 (1.157-2.169)**	**0.004**
Hypoalbuminemia	**1.576 (1.142-2.175)**	**0.006**

Abbreviations: AKI= Acute kidney injury, CI= Confidence interval, EF= Ejection fraction

DISCUSSION

Although the definition of HF has changed over the years, the current definition of the European Society of Cardiology (ESC) categorizes HF with regards to the EF range: EF ≥ 50% as HF with preserved EF (HFpEF), EF = 40-49% as HF with mid-range EF (HFmrEF) and EF<40% as HF with reduced EF (HFrEF) [19]. Signs of HF are generally related to volume overload and/or hypoperfusion. There is no specific test to diagnose HF, yet diagnosis mainly depends on history and physical examination together with certain laboratory and imaging tests. Although there is slight decrease in mortality rates with new treatments, HF related mortality rate, readmission rate and cost are still high [20,21].

In this study, we investigated the risk factors for 30-day readmission and mortality in adult patients hospitalized with a primary diagnosis of HF in a tertiary care university hospital in Turkey. All-cause 30-day readmission rate was 34.8% and HF-related 30-day readmission rate was 21.2%. Although all cause 30-day readmission rates reported in different studies are variable, they range between 20%-33% [7-10]. The rate of all-cause 30-day readmission was close to previous studies, but among them, the proportion of HF related 30-day readmission was higher than other studies. Among the heart failure patient with 30-day readmissions, less than 40% are admitted with a primary diagnosis of heart failure [6,22,23]. Hyperlipidemia, chronic liver disease, inflammatory rheumatologic diseases, malignancy, shorter length of stay and not being discharged on an ACE-i were found to be independent risk factors for HF related 30-day readmission.

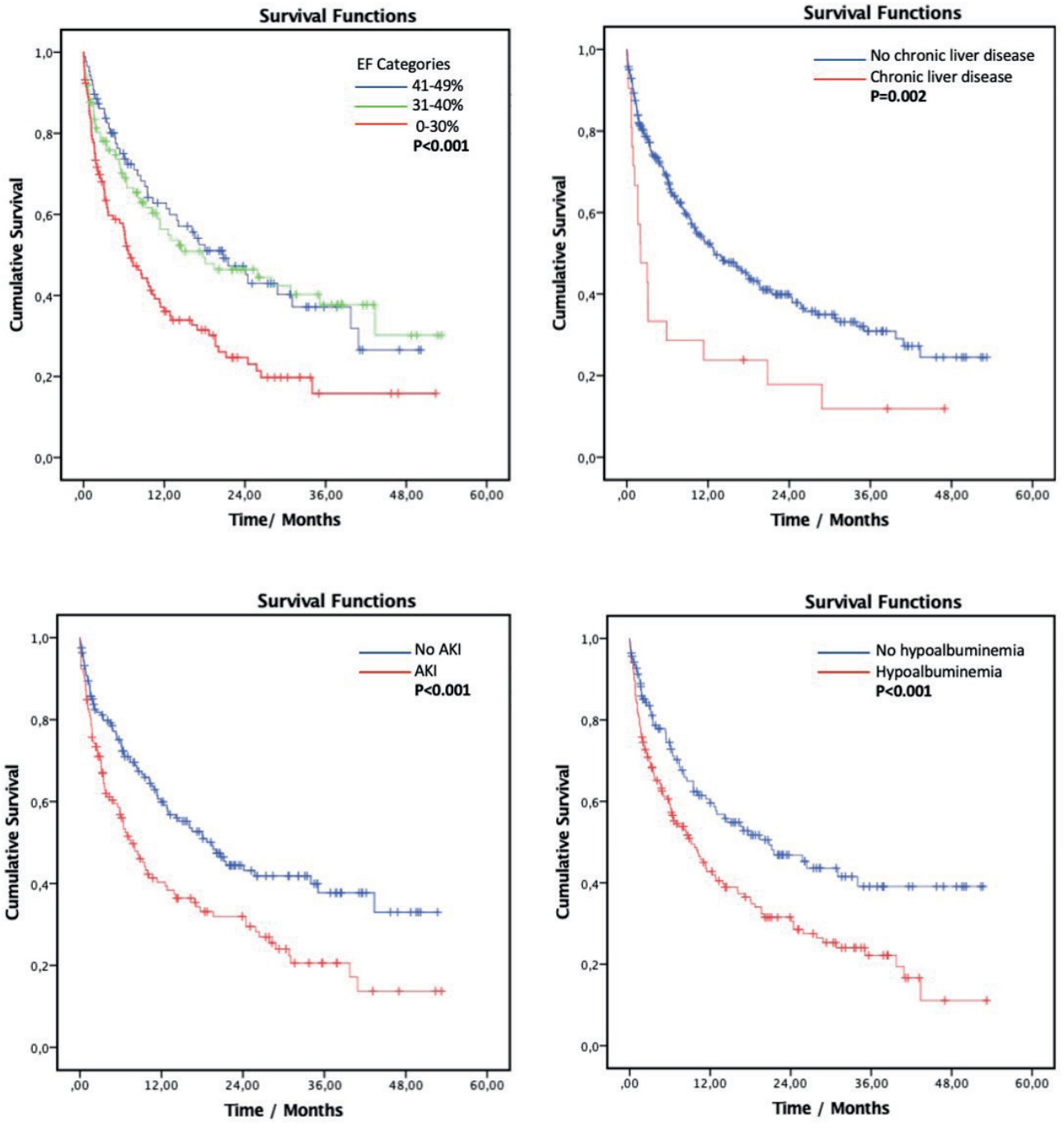

Figure 2. Kaplan-Meier curves for mortality.
Abbreviations: AKI= Acute kidney injury, EF= Ejection fraction

Having an EF<30%, chronic liver disease, AKI and hypoalbuminemia were associated with increased mortality. It's well known that increasing number of comorbidities and higher Charlson comorbidity index score are associated with poor prognosis [9,24]. Comorbidities can lead to the development of HF, as well as result in exacerbations and complications of the disease. Reduced EF is also a well-known risk factor for increased HF-related mortality [21,24]. Curtis and colleagues showed that HF-related mortality correlates closely with the level of reduction in the EF [25].

The benefit of ACE-i on HF related readmission and mortality has been demonstrated in several studies [10,26]. ACE-i not only block renin-angiotensin-aldosterone system but also prevent progressive remodeling in the heart and cause changes in neurohormonal level so improve myocyte contractility and cardiac performance [27]. Statin treatment is associated with reduced mortality in HF patients, but this study did not demonstrate a positive effect of statins on mortality [28]. Hyperlipidemia was a risk factor for unplanned readmission in this study, independent of statin

use. Unlike our study, a meta-analysis has shown that hyperlipidemia is associated with decreased mortality in patients with heart failure, but further studies are needed [29].

Although the exact mechanism is unknown, hepatic dysfunction has been found to be associated with poor outcomes and increased 30-day readmission in HF patients [8,30]. Hepatic congestion due to elevated central venous pressure and impaired hepatic perfusion due to decreased cardiac output cause hepatic dysfunction in HF patients. On the other hand, hepatic diseases such as non-alcoholic fatty liver disease are associated with development of HF and also with poor prognosis in established HF [30,31]. Functional hypovolemia despite the volume expansion and reduced systemic vascular resistance, which causes a hyperdynamic state in cirrhosis can contribute to worsening of HF [32]. Renal dysfunction accompanies more than 60% of HF patients who are hospitalized due to HF exacerbation [33]. HF patients with impaired renal function have an approximately 50% increased relative mortality risk compared to patients with normal renal function and renal dysfunction is important for risk stratification [34].

Patients with inflammatory rheumatologic diseases have higher cardiovascular disease burden than general population and most common cause of mortality in inflammatory rheumatologic diseases is cardiac diseases [35]. Inflammation is deemed to be the main contributor for the increased cardiovascular mortality, however drugs such as steroids, non-steroidal anti-inflammatory drugs and tumor necrosis factor inhibitors which target inflammation also have undesired effects on the heart [36]. In addition to these shared risk factors, patients with malignancies have other risk factors for cardiotoxicity namely therapeutic agents used in malignancies (e.g., conventional cytotoxic agents such as anthracyclines, alkylating agent; targeted therapies such as vascular endothelial growth factor inhibitors; immunotherapies) and radiotherapy [37].

Hypoalbuminemia can be a sign of cardiac cachexia, malnutrition or a consequence of chronic liver disease. Malnutrition is very commonly seen in HF patients and is found to be a prognostic risk factor for hospitalization and mortality [38]. The study from Australia was also showed that higher serum albumin levels were protective against readmission and mortality [9]. Nutritional intervention in malnourished patients have been shown to be associated with a reduced risk of HF related hospitalization and mortality [39].

Shorter length of stay was shown to be an independent risk factor for HF related 30-day readmission in our study, as Roshanghalb and colleagues also showed that longer length of stay was associated with decreased mortality and readmission rates [40]. Yet, most of the other studies demonstrated that prolonged hospitalization was associated with increased readmission rates [8,41]. Symptom severity (e.g. edema, dyspnea and poorer NYHA functional class), end organ damage (e.g. renal dysfunction and elevated troponin), comorbidities (e.g. diabetes, chronic renal disease) and social problems are the predictors of length of stay in HF patients [41-43]. Actually, prolonged length of stay can be accepted as a surrogate marker of disease severity and comorbidity burden.

As evident from our findings and from the evidence in the literature, multiple factors intervene negatively with the course of disease. The complexity of HF patients due to multiple comorbidities and polypharmacy makes it difficult to manage the patient in a fragmented healthcare system, necessitating a multidisciplinary and integrated approach [44]. Avoidable proportion of HF related 30-day readmission ranged between 5% to 79% among 16 studies, and the meta-analysis of these studies estimated that on average 23.1% of HF related 30-day readmission was avoidable [45]. Unplanned hospital readmissions, especially avoidable unplanned readmissions, are accepted as an indicator of quality of care and a hospital performance measure. Because readmissions are mainly related to previous readmission for HF, proper management of index admission is the first and most important step to prevent readmissions [46].

Pre-discharge period in the hospital, the transitional period (from hospital to home) and stable outpatient period are the main targeted time periods for interventions to reduce HF related

readmissions. As HF patients are more vulnerable in the transitional period, interventions in this period that aim to reduce unplanned hospital readmissions and mortality and improve the quality of life are promising [47]. Meta-analysis showed that transitional care programs provide reduction in all-cause mortality by 25% and HF related readmission by nearly half [48]. These programs have common components such as telephone follow-up, education, self-management, weight monitoring, sodium restriction or dietary advice, exercise recommendations, medication review, and social and psychological support. Development of congestion is the leading cause of HF decompensation and a strong predictor of poor outcome so monitoring and early detection of the congestion before decompensation is crucial [49]. Steps in transitional care programs like weight monitoring, dietary advice, medication review help prevent the congestion and telephone follow up help recognize the congestion in a timely manner. Medication adherence is one of the key points in HF treatment and interventions to improve medication compliance can reduce the risk for readmission and mortality in HF patients [50]. Unfortunately, less than half of the hospitals carry specific programs associated with transitional care in United States and this ratio is less in lower- and middle-income countries.

This study has several limitations. First of all, as it is a retrospective study and all data was obtained from patients' medical records, some factors that could have affected the disease prognosis such as drug compliance, nutritional status, physical therapy, Charlson comorbidity index and NYHA functional classification could not be assessed. Because some patients do not have TTE during hospitalization, the last TTE was taken into account. Therefore, EF at hospitalization might have been different (probably worse) from the previous EF evaluations. This is a single center study and readmissions which occurred to our hospital could be determined, so the readmission rate might be higher than calculated.

CONCLUSION

Nearly one third of patients in this cohort who were hospitalized with a primary diagnosis of HF were readmitted in the following 30 days. Having certain chronic diseases and conditions as well as a shorter length of stay were associated with an increased risk for readmission and mortality in this complex patient population. These findings point out to the special needs of HF patients, who require a proactive, integrated and multidisciplinary management strategy to control the risk factors and to improve the inpatient and transitional stages in the hospital.

Author contribution

Study conception and design: HB, MDT; data collection: HB, FC, SC; analysis and interpretation of results: HB, ECB; literature review: HB, MDT; draft manuscript preparation: HB; critical review: MDT, OAU. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Non-Interventional Clinical Researches Ethics Board (Protocol no: GO 19/349, date: 02/04/2019).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Malignancy and sarcoidosis: A single center experience from Turkey

Dorina Esendağlı[1]
ORCID: 0000-0002-6619-2952

Deniz Köksal[2]
ORCID: 0000-0001-8374-3691

Sevinç Sarınç Ulaşlı[2]
ORCID: 0000-0003-3144-7932

Salih Emri[3]
ORCID: 0000-0001-8898-8268

[1] Başkent University School of Medicine, Department of Chest Diseases, Ankara, Türkiye.

[2] Hacettepe University School of Medicine, Department of Chest Diseases, Ankara, Türkiye.

[3] Medicana Hospital, Department of Chest Diseases, İstanbul, Türkiye.

Corresponding Author: Dorina Esendağlı
E-mail: dr.dorina.de@gmail.com

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ABSTRACT

Objective: The relationship between cancer and sarcoidosis has been a research topic for a long time. An increased risk of sarcoidosis and sarcoid-like reactions is suggested in patients with malignant disease. The present study aimed to describe the clinical characteristics and the prognosis of 15 Turkish patients who had a diagnosis of both malignancy and sarcoidosis.

Methods: The patients admitted to our department between October 2013 and October 2018 were included in this study. Patient data including, the demographic data, clinical, radiological, pathological findings, and applied treatment modalities were retrieved from hospital database.

Results: The study included 14 females and 1 male with a mean age of 53.3±11.4 years. Malignancy was the preceding diagnosis in 13 patients. The mean interval time between two diagnoses was 4±3.6 years. Fourteen patients recovered from their cancer, only 1 patient with relapsed NHL was deceased. The most common type of malignancy was breast (n=7) and endometrium (n=3) carcinoma. Surgery was the primary therapeutic modality in 14 patients. Additionally patients received certain drugs which might contribute to onset of sarcoidosis such as Cyclophosphamide (n=8), Adriamycin (n=8), Trastuzumab (n=2), and Rituximab (n=1). Ten patients were asymptomatic for sarcoidosis and 7 patients had stage I pulmonary sarcoidosis. Two third of the patients (n=10) did not receive any therapy for sarcoidosis.

Conclusion: This study involves a few number of patients and according to the analysis of this group the presence of malignancy and sarcoidosis in the same patient might promote good prognosis for both entities. However the onset of sarcoidosis during the follow-up period is a challenging clinical condition and a biopsy is needed for differential diagnosis and management decision. Yet the biopsy might not be enough to differentiate between sarcoidosis and the sarcoid reactions related to malignancy. Future studies are needed to enlighten the underlying pathogenesis.

Keywords: cancer, diagnosis, drugs, malignancy, sarcoidosis.

INTRODUCTION

Sarcoidosis is a chronic granulomatous disease which can affect any organ, mainly the lungs and intrathoracic lymph nodes [1]. Despite research for many decades, the etiology of disease is not clarified yet and both genetic and environmental factors have been accused to be responsible [2]. The unknown antigen/s start a Th1 response and cause release of various cytokines. The immune system which cannot get rid of the causative agent leads to formation and maintenance of granulomas which can either resolve, persist or progress to fibrosis leading to organ dysfunction [3].

Chronic inflammation has been linked to various steps involved in tumorigenesis. The possible relationship between malignancy and sarcoidosis was first hypothesized by Brincker in 1972, who showed an association of sarcoid reaction with lymphoma in 19 patients and later on proposed the sarcoidosis-lymphoma syndrome [4]. There have been several studies from different countries with contradictory findings which tried to explain a possible relationship between malignancy and sarcoidosis [5-12]. A meta-analysis of 16 observational cohort and case-control studies including more than 25,000 sarcoidosis patients suggested a moderate association between malignancy and sarcoidosis [5]. A study from Denmark denied such a relationship and proposed that the main reason for other studies which have shown such an association is most likely due to a misclassification and selection bias [6]. Another study from USA investigating the risk of malignancy in patients with sarcoidosis in a population based cohort demonstrated that the risk was similar among patients with sarcoidosis compared to non-sarcoidosis subjects. However there was an increased risk of hematological malignancies especially among sarcoidosis patients with the extra-thoracic involvement [7].

Another important issue which can explain the association of malignancy and sarcoidosis can be the systemic granulomatous reactions which are indistinguishable from sarcoidosis that occur after use of certain drugs including cancer specific treatments like immune checkpoint inhibitors (anti-PDL-1, CTLA-4), targeted therapies (MEK and BRAF inhibitors), anti-CD20 monoclonal antibody (rituximab) and cytotoxic agents like cyclophosphamide, bleomycin, adriamycin, etc. [8].

Apart from the enigmatic association of malignancy and sarcoidosis, the onset of sarcoidosis during the follow-up period of a patient with malignancy is a challenging clinical condition. The awareness of this situation and the differential diagnosis is of great importance for further management decisions. The present study aimed to describe the clinical characteristics of 15 Turkish patients who had a diagnosis of both malignancy and sarcoidosis.

MATERIAL AND METHODS

Patients

This is a retrospective study which was performed in the Department of Chest Diseases in Hacettepe University Hospital in Ankara/ Turkey. The study included 15 patients who were admitted between October 2013 and October 2018; and followed with the diagnosis of both malignancy and sarcoidosis. The study is approved by the Clinical Research Ethics Committee of Hacettepe University (06.07.2018; GO 18/621).

A study form including the demographic data (age, gender, smoking status); medical history (history of malignant disease, medications); physical examination findings; angiotensin converting enzyme (ACE) levels; spirometry results; and radiological findings (computed tomography (CT) of thorax and/or positron emission tomography/ computed tomography (PET/CT) scan) was filled for each patient. The data were retrieved from hospital database.

The diagnosis of sarcoidosis was confirmed according to the ATS/ERS/WASOG statement (1). Only patients who belong to "highly probable" and "probable" categories were included. All the patients had a biopsy demonstrating non-caseating granulomas. Mediastinal lymph nodes (conventional transbronchial needle aspiration: 8, endobronchial ultrasonography guided transbronchial needle aspiration: 3) were sampled in 11 (73.3%) patients and extra-thoracic lymph nodes were sampled in 4 (26.7%) patients.

Statistical Analysis

Statistical analysis was conducted using the SPSS 23.0 package for Windows. Categorical variables

were shown as frequencies and percentages. Numerical variables with a normal distribution were given as mean ± standard deviation; with abnormal distribution as median and minimum-maximum.

RESULTS

The characteristics of study patients are summarized in Table 1. The study included 15 patients (14 female/ 1 male) with a mean age of 53.3±11.4 years. While malignancy was the preceding diagnosis in 13 patients, sarcoidosis was the preceding diagnosis in only 1 patient. Malignancy and sarcoidosis were diagnosed concurrently in 1 patient with endometrium carcinoma. The patient with the preceding diagnosis of sarcoidosis had both mediastinal lymphadenopathies and breast involvement (Figure 1). A biopsy of breast revealed granulomatous mastitis and one year later she was diagnosed with breast carcinoma.

Other than a patient who were actively treated with the diagnosis of relapsed Non-Hodgkin lymphoma (NHL), 14 patients were all recovered from their malignant disease and were in regular follow-up in medical oncology department. They were referred

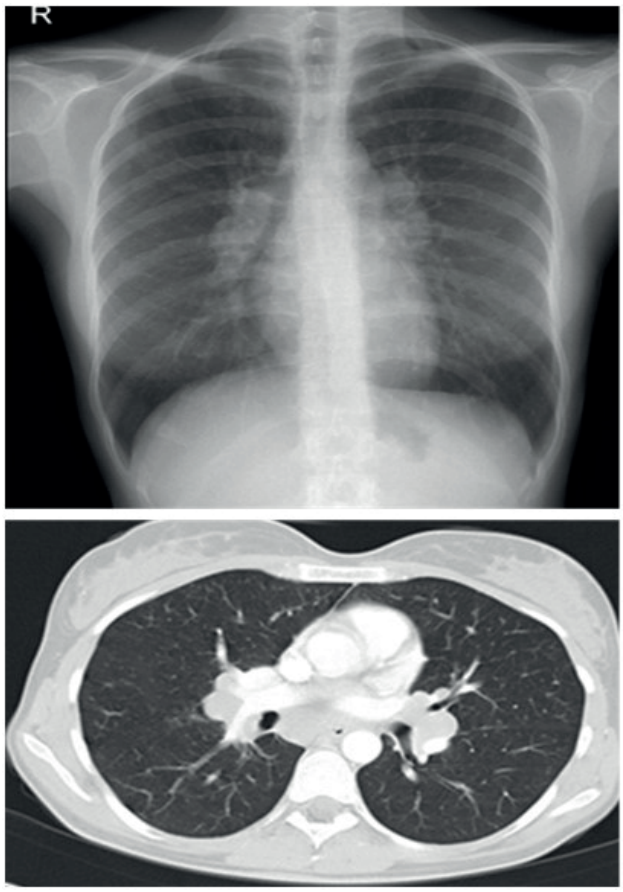

Figure 1. The x-ray and computed tomography of thorax in a patient presenting with bilateral hilar lymphadenopathy (stage 1 sarcoidosis) and also breast involvement

Table 1. The characteristics of study patients

Age	53.3 ± 11.4 years (Range:35-75)	
Gender	14 Female/ 1 Male	
Smoking history	Ex-smoker, N=7 (46.7%)	
	Non-smoker, N=8 (53.3%)	
Preceding diagnosis malignancy	N=13 (86.7%)	
Preceding diagnosis sarcoidosis	N=1 (6.7%)	
Concurrent diagnosis of malignancy and sarcoidosis	N=1 (6.7%)	
Time interval between the diagnosis of malignancy and sarcoidosis	4±3.6 years (Median: 3 years, Range: 1-12)	
History of familial sarcoidosis	None	
Mortality rate	N=1 (6.7%)	
Spirometry at diagnosis	FEV1%	FEV1%
	FVC%	FVC%
	FEV1/FVC	FEV1/FVC
Malignancy types	Breast	N=7 (46.7%)
	Endometrium	N=3 (20%)
	Rectum	N=1 (6.7%)
	Prostate	N=1 (6.7%)
	Renal cell carcinoma	N=1 (6.7%)
	Non-Hodgkin lymphoma	N=1 (6.7%)
	Adenoid cystic carcinoma	N=1 (6.7%)
Malignant disease outcome	Cured	N=14 (93.3%)
	Relapse	N=1 (6.7%)

to chest diseases department for further evaluation of new pulmonary lesions and/or mediastinal lymphadenopathies. The mean interval time between two diagnoses was 4±3.6 years (Median: 3 years, Range: 1-12 years). Only the patient with relapsed NHL died and mortality rate was 6.7% in the study population. The most common type of malignancy was breast cancer (n=7, 46.7%) and endometrium (n=3, 20%) carcinoma was the second common type. Ten patients had a PET/CT evaluation and pathological FDG uptakes ranging between 5.3 and 33 were reported in pulmonary parenchymal lesions and/or mediastinal lymphadenopathies. These high uptakes were all reported to be a possible recurrence of the previous malignant disease.

The therapeutic approaches for the malignant diseases are depicted in Table 2. Fourteen patients had undergone surgery, 7 received radiotherapy, and 9 received chemotherapy. Cyclophosphamide (n=8), adriamycin (n=8) and taxanes (paclitaxel, docetaxel) (n=5) were the most commonly used cytotoxic drugs. There were 2 patients who used trastuzumab, a monoclonal antibody used for HER2+ breast carcinoma. There was 1 patient who used rituximab, a monoclonal antibody targeting CD20 on the surface of lymphoma cells.

The clinical aspects of sarcoidosis are summarized in Table 3. Pulmonary sarcoidosis was the most common presentation, 10 patients were asymptomatic for sarcoidosis, 7 patients have stage I pulmonary sarcoidosis. Main thoracic CT findings were mediastinal lymphadenopathies and parenchymal nodules. Extra-thoracic lymphadenopathy (n=6) were the most commonly involved extrapulmonary site of sarcoidosis. Two third of the patients (n=10) did not receive any therapy for sarcoidosis. While 4 out of 10 patients who did not receive any therapy had spontaneous remission, 6 patients had a stable disease.

Table 2. The therapeutic approaches for the malignant diseases

Therapeutic approach			
Surgery	N=14		
Radiotherapy	N=7		
Chemotherapy	N=9		
Chemotherapeutic agents			
Cyclophosphamide		Hormone therapy	
Adriamycin	N=8	Tamoxifen	N=1
Paclitaxel	N=8	Anastrozole	N=2
Docetaxel	N=4		
Vincristine	N=1		
5-Fluorouracil	N=1		
Trastuzumab	N=1		
Rituximab	N=2		

DISCUSSION

This study describes the clinical features of 15 Turkish patients diagnosed with both malignancy and sarcoidosis. The majority of patients were female (n=14) and the most common type of malignancies were breast and endometrium carcinoma. Malignancy was the preceding diagnosis in most of the patients (n=13) and the mean interval between the two diagnoses was 4±3.6 years. Most of the malignancies were cured (n=14). Majority of the patients (n=10) had asymptomatic sarcoidosis. Nearly half of the patients had stage I pulmonary

Table 3. The clinical aspects of sarcoidosis in the study patients

Clinical aspect		N (%)
Involved systems	Pulmonary	14 (93.3)
	Extra-pulmonary	7 (46.7)
Pulmonary sarcoidosis stage	I	7 (46.7)
	II	6 (40)
	III	1 (6.7)
Involved extra pulmonary sites	Extra-thoracic lymphadenopathy	6 (40)
	Liver	1 (6.7)
	Spleen	1 (6.7)
	Breast	1 (6.7)
Thorax CT findings	Lymphadenopathies	13 (86.7)
	Nodules	6 (40)
	Micro nodules	2 (13.3)
	Bronchiectasis	1 (6.7)
Symptoms	Asymptomatic	10 (66.7)
	Symptomatic	5 (33.3)
Laboratory	Elevated ACE	4 (26.7)
Treatment	No treatment	10 (66.7)
	Steroid	4 (26.7)
	Steroid + methotrexate	1 (6.7)
Treatment response	Remission	2 (13.3)
	Stable disease	1 (6.7)
	Relapse	2 (13.3)
Follow-up of untreated patients	Spontaneous remission	4 (26.7)
	Stable disease	6 (40)

sarcoidosis. The main thoracic CT findings were mediastinal lymphadenopathies and parenchymal nodules. The prognosis of sarcoidosis was good and two third of the patients (n=10) did not receive any therapy.

The relationship between malignancy and sarcoidosis has been described in various publications [5-13]. However it is still unclarified whether this relationship is by chance, by an underlying mechanism such as chronic inflammation and dysregulated immune surveillance, or by a genetic predisposition that can explain the concurrent presence of two diagnoses in the same patient. Sarcoidosis and sarcoid like reactions have been encountered in different types of malignancies and both the distribution and frequency vary among different countries. Lymphoma, breast, testicular, gastrointestinal and lung carcinoma are the most common types of malignancies that are related with higher frequency of sarcoidosis [14-18]. In most of the studies, the diagnosis of sarcoidosis was usually made after a long period (more than 5 years) of malignancy diagnosis [9]. However, in a recent study 66% of sarcoidosis cases were diagnosed within the first year of malignancy diagnosis [19]. In the present study, breast (46.7%) and endometrium carcinoma (20%) were the most common malignancies and the mean time interval between two diagnoses was 4±3.6 years ranging between 1 to 12 years. The main reason that might influence the type of malignancy can be the gender differences among different studies as seen in the present study with female predominance and breast carcinoma relatedly. The incidence of sarcoidosis in females has a biphasic pattern with the first peak at 25-39 years and the other in 50-60s. The mean age of the patients in our study was 53.3 years which is similar to the literature and compatible with the second peak observed in females in general population supporting the coincidence of sarcoidosis and malignancy.

In cancer patients granulomas can be detected mainly in 2 clinical scenarios. The first one is the sarcoid reactions most commonly occurred in the lymph nodes draining the tumor and other organs such as spleen, skin and bone marrow. The second is the typical sarcoidosis presentation. While the first scenario is usually asymptomatic, the second can be symptomatic. The mechanism of tumor associated sarcoid reactions in regional nodes has not been elucidated, although some authors have suggested that the relationship between a malignancy and a sarcoid reaction is a reaction of host resistance to the tumor or a reaction to metabolic disintegration substances released from the tumor cells [20]. Interestingly all the cases of the study except one had their cancer in remission thus questioning the possibility of host immunity against a cancer that was not active and supporting the typical sarcoidosis presentation. On the other hand it should not be underestimated the fact that malignancies can relapse even after a long period of time and this study included at most a 12-year long period of follow-up.

Another issue which might explain the relationship are the treatment modalities used for the malignant disease. Several chemotherapeutics (bleomycin, vinblastine, cyclophosphamide, adriamycin), immune checkpoint inhibitors (nivolumab, pembrolizumab), targeted therapies (BRAF and MEK inhibitors), and monoclonal antibodies (rituximab, trastuzumab) can cause sarcoidosis and sarcoid like reactions [8,21-23]. In the present study, similar to the Japanese series, surgery was the primary therapeutic modality in 14 patients [14]. Additionally patients received certain drugs which might contribute to onset of sarcoidosis such as cyclophosphamide (n=8), adriamycin (n=8), trastuzumab (n=2), and rituximab (n=1). None of the patients used immune check point inhibitors.

Sarcoidosis subsequent to diagnosis of malignancy has been related to a favorable prognosis, remission of cancer, and low frequency of relapse thus suggesting an immune response that might help to keep the malignancy under control in these patients [15-16,24]. A retrospective multicenter observational study enrolling 133 patients with a confirmed diagnosis of cancer and subsequently developed granulomas in different organs have shown that there is a significant association between the presence of granulomas and reduced metastasis and increased survival [25]. The present study even though including a few number of patients also supports these findings by demonstrating recovery from malignant disease in 14 patients. In the current literature, there is insufficient data related to the clinical presentation and prognosis of sarcoidosis in patients with a preceding diagnosis of malignancy. In our series,

most of the patients (n=10) had asymptomatic sarcoidosis. Nearly half of the patients had stage I pulmonary sarcoidosis. The clinical outcome of sarcoidosis was similar to the general population and two third of the patients (n=10) did not receive any therapy for sarcoidosis. Whether the presence of a previous malignancy serves as a protection and results with a mild clinical presentation for sarcoidosis is a matter that needs to be clarified.

FDG-PET/CT is a widely used imaging modality for staging and follow-up of various tumors [26]. It is useful for the detection of lymph node metastasis, but false-positive results can occur due to sarcoidosis. Therefore sarcoidosis should be considered in differential diagnosis when newly emerging lymphadenopathies or lung lesions appear, and a biopsy should be performed for differential diagnosis and further management decisions. Endobronchial ultrasonography guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive way for demonstrating non-caseating granulomas in mediastinal lymph nodes [25]. Retrospective studies have shown that sarcoidosis/ sarcoid-like reactions are seen more commonly in restaging PET/CT in patients with suspected relapse rather than initial staging. This observation suggest that this phenomenon may be related to an anti-neoplastic immune response that represents a host defense mechanism against the spread of tumor cells. This theory is supported by the finding that sarcoid-like reactions are associated with better prognosis in patients with gastric cancer and Hodgkin's lymphoma [27]. The present study also supports this finding with 14 patients who recovered from their cancer. All PET/CTs were performed for regular follow-up or suspected relapse. Conventional or EBUS-TBNA were the most commonly used biopsy methods for differential diagnosis.

The class II major histocompatibility complex (MHC) molecules encoded by human leukocyte antigens (HLA) play an important role in antigen presentation. It has been shown by many studies from different countries including Turkey that HLA alleles are closely related to the risk of developing sarcoidosis, the type of clinical presentation, extra-pulmonary involvement and the outcome of disease [28-29]. To our knowledge there has been no study that has investigated the relationship of HLA and the risk of cancer in sarcoidosis patients, which could also enlighten the genetic effect that might play a role in pathogenesis. According to the data of some cancer patients (n=13) who were included in our previous study HLA-DQB1*03 was the most common allele in cancer patients (unpublished data). Further studies including the HLA genotyping of the cancer-sarcoidosis entity should be performed in order to enlighten the mystery beyond the relationship of the two diseases and the pathogenesis of sarcoidosis which up-to-date is still unknown.

The major limitations of the study are the retrospective nature of the study, the low number of patients included and the absence of a control group. However the present study is the first case series from Turkey with 15 patients who had a diagnosis of both malignancy and sarcoidosis. Moreover this study represents a comprehensive examination of whole study patients with a long follow up period. Yet it is still not very clear the cut off criteria for the differentiation of the sarcoidosis and the sarcoid-like reactions in patients with malignancy which might be a subject of changes in evaluation of the entities in the future. Bonifazi et al. proposed a diagnostic work-up for cancer patients with an identification of granuloma on biopsy and stated that elevated ACE, granulomas in areas remote from cancer, previous diagnosis of sarcoidosis, atypical involvement for cancer (ocular, skin, parenchymal lung disease and cardiac) and hypercalcemia with high vitamin D1,25 and low vitamin D25 and PTH are features that favor sarcoidosis rather than a relapse of the malignancy [30].

CONCLUSION

By analyzing the data of the 15 patients that have been followed up in our center for 5 years we have demonstrated that the presence of cancer and sarcoidosis in the same patient might promote good prognosis for both entities. Although the onset of sarcoidosis during the follow-up period is a challenging clinical condition, the awareness of this coexistence and appropriate differential diagnosis are of great importance for further management

decisions. Usage of certain drugs can be a clue for onset of sarcoid reactions. Future studies are needed to enlighten the exact pathogenesis and probable role of HLA alleles.

Author contribution

Study conception and design: DE, SE; data collection: DE, SSU, DK; analysis and interpretation of results: DE and DK; draft manuscript preparation: all the authors. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Hacettepe University (Protocol no. 18/621 / 06.07.2018).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Older patients' driving safety with the help of DRIVING SIMULATOR: Which cognitive test can predict better driving safety?

Mert Eşme[1]
ORCID: 0000-0003-3617-2077
Orkun Tahir Aran[2]
ORCID: 0000-0002-5468-1302
Cafer Balcı[3]
ORCID: 0000-0002-1478-1106
Ege Temizkan[4]
ORCID: 0000-0002-8275-1777
Serdar Ceylan[3]
ORCID: 0000-0001-5885-4023
Meltem Koca[3]
ORCID: 0000-0003-3013-8556
Arzu Okyar Baş[3]
ORCID: 0000-0002-1518-5939
Berkan Torpil[5]
ORCID: 0000-0002-0322-5163
Onur Altuntaş[4]
ORCID: 0000-0002-2403-2096
Mine Uyanık[4]
ORCID: 0000-0002-4504-7481
Meltem Halil[3]
ORCID: 0000-0001-7597-8140
Mustafa Cankurtaran[3]
ORCID: 0000-0002-8213-7515
Burcu Balam Doğu[3]
ORCID: 0000-0002-4430-6146

[1] Mersin City Training and Research Hospital, Geriatrics Clinic, Mersin, Türkiye.

[2] Hacettepe University Faculty of Health Sciences, Occupational Therapy, Ankara, Türkiye.

[3] Hacettepe University, Faculty of Medicine, Faculty of Medicine, Department of Internal Medicine, Division of Geriatrics, Ankara, Türkiye.

[4] Hacettepe University, Faculty of Health Sciences, Occupational Therapy, Ankara, Türkiye.

[5] Health Science University of Türkiye, Faculty of Gülhane Health Sciences, Department of Occupational Therapy, Ankara, Türkiye.

Corresponding Author: Mert Eşme
E-mail: mertesme87@hotmail.com

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ABSTRACT

Introduction: Being able to drive is an important parameter of independence and self-sufficiency. The continued use of cars, which plays an important role in maintaining the mobility of the older individuals, is very important for the protection of the individual's activity performance.

Methods: Driving skills of 31 participants were tested with the help of a driving simulator and cognitive tests were applied to each participant. The study was aimed to reveal the relationship between the cognitive functions and safe driving skills of older patients using the driving simulator and to determine the cognitive test that predicts the safe driving skill best.

Results: 31 participants was included in the study. All participants were male. The average age was 72.5±6.The median of MMSE was 29 (IQR; 28-30),the mean of MOCA was 25.52±2.6,the mean value of QMCI was 62.68±9.57, the median of trail making test A was 42.5 sec(22-97), and the median of trail making test B was 98.31 sec(38-313).MOCA test score correlated positively with "the skills expected before starting the vehicle "and driving parameters on the highway("p: 0.0024, r:0.46";"p:0.0024, r:0.46",respectively).The QMCI test was found to have a statistically positive and significant correlation with operational skills and the skills expected before starting the vehicle("p:0.041, r:0.43"; "p:0.015 r:0.50",respectively).When the factors affecting operational skills and safe driving skills were analyzed by linear regression analysis, both skills were influenced by the QMCI-orientation step(p:0.001;CI:1.59-3.9).

Conclusion: In our study, it is shown that driving skills decrease with aging. QMCI and MOCA, which are easy to apply in clinical practice, will be useful in patients driving vehicles aged 65 and over with the demonstration of a significant relationship with total driving score, safe driving and operational skills.

Keywords: driving, simulator, cognitive, older.

INTRODUCTION

Aging is a process that negatively affects many systems. Mobility is an integral part of these systems and is an indispensable element of the independence and quality of life of older individuals. The limitation of mobility causes problems in the daily living activities of older individuals and these problems also negatively affect their mental and cognitive functions [1,2]. Being able to drive is an essential parameter of independence and self-sufficiency in today's conditions. In this sense, the continued use of cars, which plays an important role in maintaining the mobility of older individuals, is crucial for protecting the individual's activity performance [3].

It has been shown in studies that the decrease in visual, motor, and cognitive functions has an influence on the reduction in driving safety [4]. The gold standard method that will best test driving safety is the test in which driving abilities are evaluated in a real vehicle. However, performing a real driving test is technically difficult and has some safety problems [4]. Driving simulators offer an option to assess both safety and deficiencies in this regard. Driving simulators are safe alternatives used to evaluate the driving skills of people at risk in terms of safe driving skills without being exposed to risks [5]. Simulation devices can also be used in the rehabilitation/training of drivers at risk [5].

The aim of our study was to reveal the relationship between the cognitive functions and safe driving skills of older patients using the driving simulator and to determine the cognitive test that predicts safe driving skills best.

METHOD

Subjects

Patients aged 65 years or older who applied to the Geriatric medicine outpatient clinic and who were active drivers in the last 6 months were included in the study. Informed consent was obtained from each patient before inclusion in the study. Exclusion criteria were patients;

- who did not have a driver's license,
- had diagnosed with conditions that legally restricts driving such as dementia, diplopia, epileptic seizures etc
- had comorbidities such as hearing and visual deficits or neurological diseases that might affect driving,
- had been using of sedatives or psychiatric drugs
- did not drive in the last 6 months despite having a driver's license were excluded from the study.

Components of the comprehensive geriatric assessment were applied to all participants. The independence levels of all patients in their daily lives were evaluated with Katz index of activities of daily living (ADL) test and Lawton Brody Instrumental activities in daily living scales (IADL) [6]. For cognitive assessment, Mini-Mental State Examination test (MMSE), Montreal Cognitive Assessment Test (MOCA test), Quick Mild Cognitive Impairment Screen (QMCI test), Forward and backward digit span Test, Trail Making Test A and B, and clock drawing test (6 points) were performed. Risk of falls were assessed by Timed up and go test and Alternating foot tap test.

Assessment of Activities of Daily Living

The Katz scale evaluates everyday activities that are fundamental. The Katz ADL scale is sensitive to changes in deteriorating health status. It helps healthcare professionals involved in the patient's holistic care to speak the same language about their function [7]. The Katz ADL assesses a person's dependence or independence with regard to six ADL areas: dressing, using the restroom (sponge, shower, or bathtub), bathing (shower, bathtub), transference, continence, and feeding. Every activity is divided into three categories on the original scale: independence, partial dependency, and complete dependence. In accordance with this classification, as independence increases the score of the scale increases [8].

Cognitive assessment

The MMSE is the most commonly used screening test for dementia screening [9]. The MMSE is evaluated out of 30 points and below 24 points

indicate cognitive impairment and indicates the need for further evaluation. It is an easy and fast scale that tests orientation, memory, attention, calculation, recall, language, motor function, perception, and visuospatial abilities [10].

Another cognitive assessment test is the MOCA test [11]. It was developed as a rapid screening test for mild cognitive impairment. MOCA assesses different cognitive functions. These conditions are attention and concentration, executive functions, memory, language, visual construction skills, abstract thinking, calculation, and orientation. The highest total score that can be obtained from the test is 30. Accordingly, a score of 21 points or more is considered normal [10]. Turkish validity and reliability study was conducted [12].

The Q-MCI test is a scale that is more sensitive than the MMSE in distinguishing mild cognitive impairment from subjective forgetfulness and early-stage dementia [13]. In the study, in which the Turkish validity and reliability were evaluated, it was shown that the Q-MCI is superior to MMSE and similar with MOCA in distinguishing mild cognitive impairment [14]. The test consists of 6 different subtests. The first subtest relates to testing orientation. The patients are asked questions such as the day, month, year, and name of the country in which they are living. The second subtest relates to testing word recording. The patients are told 5 words and asked to repeat these 5 words. The third subtest is the clock drawing test. It is different from the clock drawing test mentioned above in terms of calculation. In total, the maximum score to be obtained from the clock drawing test is 15. The fourth subtest is delayed recall. In the fourth subtest, the patients are asked how many of the 5 words they remember. The fifth subtest is verbal fluency. In one minute, the patients are asked to name as many animals as possible. The sixth and the last subtests is related to logical memory. A short story is read to the patient. When the story is over, it is questioned how many of the words used in the storytelling are remembered. The total of six subtests is scored on 100 points [10]. For the QMCI test, the closer the score is to 100 points, the better cognitive performance can be considered.

As quick clinical assessments of WM, the Wechsler Memory Scale—Third Edition's Digit Span subtest have been widely used [15]. The tasks contain a forward and a backward component and call for the recall of the stimulus (digits or spatial locations) in the examiner's order, or in the opposite order. It has been suggested that the forward digit span is a measurement of the phonological loop's capacity, and that the forward spatial span is a comparable indicator of the visuospatial sketchpad [16]. It has been suggested that successful completion of the backward component of these tasks is a test of central executive function due to the additional demand of manipulating information in temporary storage [17].

Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered between 1–25, and the patient is required to draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters [18]. The scoring of the both tests are based on time elapsed for completion; for the part A, a completion time longer than 32 seconds [19] and for part B completion time longer than 79 seconds considered as problematic in terms of driving safety [20].

Another test that shows deterioration starting from the early stages of dementia is the clock drawing test [21,22]. The patient is asked to draw the face of the clock as a round shape in which he can write the numbers. The patient, who is asked to place the numbers as they are on the wall clock, gets 3 points from the correct placement of the circle and the number 12. Placing other numbers in appropriate places is 1 point. Drawing the hands of the clock is 1 point. Correct placement of the hour and minute hands according to the desired time is again 1 point. In this way, the patient is evaluated over 6 points. With this test, constructional praxis, understanding, and planning ability are tested [21,22].

Motor functioning

Another test we applied to our patients was the "timed up and go test". The patient should sit in a standard chair, lean back against the chair, and rest his arms on the arms of the chair. The patient should walk in a line 3 meters (9.8 feet) away, then walk back to the chair and sit down. The test ends when the patient's hip touches the seat. A stopwatch should be used to time the test [23]. According

to Physician's guidelines [24] to assessing and counseling older drivers, scores over 9 seconds are linked to a higher risk of motor vehicle tasks that are negligent [25].

The last test we applied to the patients was "alternating foot tap test". This test is an alternative test that allows the driver to measure the time it takes to move their right foot from the accelerator pedal to the brake pedal. The driver sits in a chair for this test. The test administrator opens a 2-inch 3-ring folder and places it on the floor with the 3 rings diagonally in front of the participant and 16 to 24 inches from the front edge of the chair. Following the instructions, the tested patient will touch the ground alternately with their right foot 5 times on either side of the open file and move from side to side with each touch. The total number of hits will be 10. The examiner records the time to complete the foot tapping task with a stopwatch [26]. The Alternate Foot Strike test is a test that measures a person's ability to quickly move their leg/foot from the accelerator pedal to the brake. Elevated traffic conviction rates (1.5 times age-matched controls) were found in those with response times exceeding 12.75 seconds [27].

Driving safety assessment

AutoSim AS1000 Driving Simulator, Norway [28] was used for driver evaluation in a simulated environment. This simulator has a real car cockpit and the image is able to provide a 180-degree viewing angle through 3 combined widescreen monitors. With its software containing different traffic situations, the simulator provides the evaluation of older patients in various environments and situations that require sudden decisions. In our study, compliance with traffic rules and accurate driving behavior were evaluated observationally during the application. During the observational evaluation, the task list was prepared by making use of the car driving requirements in the literature [29-31]. Driving was evaluated under the headings of "the use of vehicle operational parts and safe driving behavior". A detailed representation of what participants are expected to do in the driving test are given in Table 1. In the context of the use of operational parts, skills such as adjusting the mirror and seat settings, fastening seat belts, learning the location of vehicle operation controls, gear control, pressing the brake pedal, and operating the car properly were included. In the content of the safe driving behavior part, the signal, control of the lane to be exited, stopping the vehicle in the right lane and on the ground, signal, deceleration, protecting the lane, awareness pedestrian priority, noticing danger, signal, mirror control, changing lane, control of signals, vehicle positioning, and safe tracking distance were examined. The skill parameter(s) that individuals made wrong were marked as 0 points and correct behaviors marked as 1 points. Before the evaluation, individuals

Table 1. Skills that participants are expected to perform in the driving test.

THE USE OF VEHICLE OPERATIONAL PARTS	**The skills expected before starting the vehicle**	adjusting the mirror and seat settings	Fastening seat belts	learning the location of vehicle operation controls,	
	Start the vehicle	gear control,	pressing the brake pedal	operating properly	
SAFE DRIVING BEHAVIOR	**Movement**	the signal	Lane control		
	Stopping	stopping the vehicle in the right lane and right side			
	Turns	The signal	deceleration, protecting the lane	knowing pedestrian priority,	noticing danger
	Changing lane	signal	Mirror control,	Changing lane	
	Safety behavior	Mirror control	control of signals and lamps	vehicle positioning	safe tracking distance
DRIVING PARAMETERS ON THE HIGHWAY		Adjusting the speed,	Lane tracking		
TOTAL					

used a simulation environment for 10 minutes to get used to the simulation environment without any orientation. The application was started from the beginning for evaluation and the patient was informed about observation. In two-way city traffic, a driving assessment was performed on the 30-minute track, which included unexpected 3 sudden stops, lane change, lane return, parallel parking, and driving uphill. Participants were then told to move to the highway section, and it was observed whether they complied with the highway traffic rules and speed limits, and the record was obtained. The driving points of the participants were calculated according to the observation form.

Visual and hearing deficits

Whisper test was performed on each patient from 6-7 meters and hearing dysfunction was determined. Likewise, with the vision test, the patients' visual functions were evaluated and they were asked to bring visual aids such as glasses, if any.

Statistical analyses

Statistical analyses were performed using IBM SPSS version 22 software. The conformity of the variables to normal distribution was examined with histogram and probability graphs and Kolmogorov-Smirnov/Shapiro-Wilk tests. For descriptive analysis, mean and standard deviation were used for normal variables. For the non-normally distributed variables, the median and minimum-maximum values were used. Pearson test was used to evaluate the correlations of normally distributed numerical variables with each other. Spearman test was used for numerical variables that were not normally distributed. Correlation relationships between cognitive tests scores and driving tests scores were analyzed by Spearman correlation analysis. The independent effects of different predictors on driving safety tests were investigated using a multiple regression model. Factors affecting driver behavior were analyzed by linear regression analysis. Model fit was examined using the required residual and fit statistics. The suitability of the regression model and residual analyzes were performed. The variables included in the model were evaluated by colinarity analysis. Cases with a type-1 error level below 5% were interpreted as statistically significant.

RESULTS

Fifty participants were included in the study initially. Nineteen did not want to attend the driving simulation due to personal reasons. These participants didn't come because they did not want to spare time for the study. Finally, the study was conducted with 31 patients. All of the participants were male. The mean age was 72.5 ± 6.0 years. Participants were driving license holders for 40.9 ± 11.3 years. Considering the education levels of the participants, the median was 11 years (IQR, 11-15 years). Other demographic results and cognitive test results are shown in Table 2.

The median number of accidents of the participants was 0 (IQR, 0-1). Nineteen patients had no previous history of an accident. It was learned that none of the accidents were fatal accidents.

The median of MMSE of the participants was 29 (IQR, 28-30), the mean of MOCA was 25.5 ± 2.6, the mean value of QMCI was 62.68 ± 9.57, the median of the trail-making test A was 42.5 sec (22-97), and the median of the trail-making test B was 98.3 sec (38-313 sec). It was observed that the MOCA test score correlated positively moderately with "the skills expected before starting the vehicle" and driving parameters on the highway ("p: 0.0024; r: 0.46"; "p: 0.0024; r: 0.46"; respectively). The QMCI test had a statistically significant, positive, and moderate correlation with operational skills and the skills expected before starting the vehicle ("p: 0.041, r: 0.43"; "p: 0.015 r: 0.50", respectively). The relationship between driving parameters and these cognitive scales is shown in Table 3. The QMCI test was found to have a statistically significant and strong correlation with safety behavior parameters (mirror and seat adjustment, seat belt wearing, and learning the location of vehicle operating controls before starting the vehicle) (p: 0.041, r: 0.70). With increasing age, there was a decrease in operational skills, skills that were expected to be signaled and control of the lane to be exited, and skills expected to be carried out before starting the vehicle. This negative relationship was statistically significant ("p: 0.012 r: -0.50"; "p: 0.002 r: -0.60", "p: 0.005 r: -0.55" respectively). It was seen that as the education level increased, lane control skills and signaling skills increased accordingly (p: 0.042, r: 0.40). These correlations are shown in Table 4. It was seen that

Table 2. Cognitive test scores and comorbid diseases of the participants included in the study with demographic data.

Age	72.5 ± 6.0	**Number of using drugs**	2 (0-7)
Education Level			
Primary School	1 (3.2%)		
Junior High School	4 (12.9 %)		
High School	12 (38.7%)		
University	13 (41.9%)		
Diabetes Mellitus	10 (32.3%)	**vehicle use experience (years)**	42 (24-68)
Hypertension	13 (41.9%)	**Daily Living Activities**	6
Coronary artery disease	7 (22.6%)	**Instrumental daily living activities**	8
Cerebrovascular event	1 (3.2%)	**Previous traffic accident**	12 (38.7%)
Chronic Obstructive Lung Disease	1 (3.2%)	**MMSE**	29 (IQR ; 28-30)
Atrial Fibrilation	1 (%3.2)	**MOCA**	25.52 ± 2.6
Hyperlipidemia	8 (25.8%)	**QMCI**	62.68 ± 9.57
Hypothyroidism	3 (9.7%)	**Trail Making Test A**	42.5 sec (22-97)
Osteoporosis	0	**Trail Making Test B**	98.31 sec (38-313)
		Alternate Foot Tap Test	5.3 (3-9)
		Up and Go Test	11.87 ±2.4

Table 3. Correlation relationship between MOCA and QMCI tests and driving parameters.

	MOCA P value and CC	QMCI P value and CC
the skills expected before starting the vehicle	P: 0.0024 r: 0.46	p: 0.015 r: 0.50
driving parameters on the highway	P: 0.0024 r: 0.46	-
operational skills	-	p:0.041 r: 0.43
safety behavior parameters	-	p: 0.041, r: 0.70

*CC: Correlation Coefficient, MOCA: Montreal Cognitive Assesment Test, QMCI : Quick Mild Cognitive Impairment Test

Table 4. Correlation of age and education level with driving skills.

	Operational skills	Skills that were expected to be signaled and control of the lane to be exited	The skills expected before starting the vehicle
Age	p: 0.012; r: -0.50	p: 0.002; r: -60	p: 0.005; r: - 0.55
Education level	**Lane control skill** p: 0.042, r: 0.40		**Signaling skills** p: 0.042, r: 0.40

the backward digit span test, which is very simple and practical to apply in clinical practice, correlates positively with operational skills. In the unadjusted model, QMCI was found to be associated with operational skills (p: 0.025; OR: 0.36 CI: 1.14-1.70)

When the factors affecting the total scores obtained after simulation was analyzed by multivariate linear regression analysis; age, backward digit span test, and MOCA- naming step were found to be factors affecting the simulation total score (p: 0.005 CI: -1.2 / -0.3; p: 0.001 CI: 0.6 / 0.9; p: 0.002 CI: -6 / - 2). The result of the regression analysis is shown in Table 5. Multivariate linear regression analysis was performed to determine the factors affecting the skills expected before starting the vehicle. When QMCI, MOCA, age, MOCA-orientation step, and year of education were included in the model, it was seen that the orientation step in the MOCA test was a factor affecting "the skills expected before starting the vehicle" (p: 0.0001 CI: 1.969-3.728). When the factors affecting operational skills and safe driving skills were analyzed by linear regression analysis, it was seen that both skills were influenced by the QMCI-orientation step (p: 0.001 CI: 1.59-3.9).

Table 5. Factors affecting driving score with multiple regression analysis.

	Unstandardized Coefficients		Standardized Coefficients	t	P value
	B	Std. Err	Beta		
Age	-0.840	0.175	-0.455	-4.807	p: 0.005
MOCA- naming step	-4.295	0.702	-0.596	-6.121	p: 0.001
Backward digit span test	1.045	0.145	0.693	7.205	p: 0.002

*MOCA: Montreal Cognitive Assesment Test

DISCUSSSION

Older adults consider driving an important activity for their independence and self-confidence [32,33]. Older adults who are forced to stop driving become more dependent on their families, often become depressed, and, as a result, reduce their social activities. Ultimately, the risks of being placed in a nursing home are high [34]. For this reason, it is important to detect the decline in driving abilities in the early period in order to maintain the independence of the older adult. In this study, we wanted to examine the usability of the driving simulator device and the relationship between the driving skills that this device can predict and cognitive functions in order to ensure the continuation of the gains necessary for our patients to maintain their independence.

Physiological limitations and decreases in activities of daily living can be seen with aging. In today's conditions, the use of a vehicle for transportation from one place to another is considered one of the basic needs. The deprivation of this basic need of older people or the fact that they can no longer use the vehicles they used to do in their youth may cause a fragility, which will negatively affect their independence in daily life in many aspects, especially in social participation and independence in outdoor activities. In this study it was found that safe driving is highly associated with cognitive functions, education level, and age.

As the proportion of the older population increases, the proportion of older drivers also increases. A 2018 study showed that there are 29 million drivers over the age of 70 in the United States [35]. According to statistical data, more than 8,000 drivers over the age of 65 died in 2018, and more than 250,000 older drivers were hospitalized and treated in hospitals. [36]. When this rate is calculated on a daily basis, it should be considered that 20 older drivers lose their lives due to accidents almost every day.

It is difficult to understand, determine or measure whether an older driver can drive safely. Chronological age cannot be the only indicator of driving ability. It is hard to consider that driving abilities, brake time, or the ability to make decisions in risky situations of a 70-year-old, non-sarcopenic older individual without any chronic disease and an older individual with the opposite clinical condition are the same. Due to this complex side of driver evaluation, there are no easy-to-administer test or set of tests to assess driving proficiency [37-39]. For this reason, cognitive test methods that can be used to predict effective and safe driving ability were investigated in our study. It has been observed that there is a direct relationship between total driving scores and cognitive test scores, and between some other driver ability parameters and cognitive tests.

Older drivers have a higher death rate in vehicle accidents than other driver age groups. Among the older drivers, the group over the age of 85 has the highest number of fatal accidents [40]. Fatal accident rates begin to increase after age 70 [35]. It has been observed that the probability of being at fault in fatal intersection accidents is generally higher in older drivers [41]. Among the most common mistakes are incorrect assessment of vehicle distance and speed, medical events, daydreaming, and inadequate surveillance [41]. In our study, we did not have any patients who participated in an accident that would pose a life-threatening risk or an accident that resulted in death. Since a control group was not selected as the young patient profile that we can compare, it would be assertive to suggest that the age factor increases the risk of accidents. However, it has been shown in our study that the safe driving skills score has a negative correlation with age.

Aging negatively affects muscle strength especially in the neck, shoulder, and wrist, and brake reaction time [42]. As a result of reduced muscle strength,

operational aspects of driving are negatively affected. Restrictions in the neck, shoulder, and wrist movements can limit vision and the ability to control the steering wheel. Sensory and/or motor neuropathy is common in older adults and may impair brake and accelerator pedal use [43]. In addition to age-related changes such as visual disturbances and reduced psychomotor abilities, older people are more likely to have medical illnesses that may affect their ability to drive. Studies have identified specific medical conditions associated with vehicle accidents or events that may adversely affect driving safety in the older population. History of falling in the last 1-2 years [44], disorders in cognitive and visual functions [45-49], history of previous accidents [45,50], presence of opioids, benzodiazepines, and tricyclic antidepressant groups among drug use [51,52], age-related diseases such as dementia, Parkinson's disease [53,54] are among the risk factors. More than a third of all prescribed benzodiazepines are written for people 60 years and older. Traffic accident risk increases by 50 percent in the first week after benzodiazepine treatment [55]. In a different study examining hospitalizations of older patients after vehicle accidents, it was found that the risk of serious accidents associated with the use of benzodiazepines increased fivefold. It has also been shown that antidepressants increase the risk 1.8 times, and opioids 1.5 times [56]. In our study, it was not shown that the chronic diseases of our patients were a risk factor that would reach statistical significance in terms of driving safety or driver score. The reason for this is the low number of patients, which is another limitation of our study. Since we did not have the usage record of benzodiazepines and tricyclic antidepressants, no evaluation was made in this respect. Since dementia and Parkinson's disease diagnoses were also determined as exclusion criteria in our study, risk assessment was not performed.

The incidence of dementia increases with the prolongation of the average lifespan. According to the research conducted by the Alzheimer's Association, the number of patients with AD, which was 5.2 million in 2014, is expected to increase to 13.8 million in 2050 [57]. In a study examining the effect of cognitive functions on driving abilities, it was shown that patients with very mild or mild dementia were more likely to fail the driving test than patients without dementia [58]. In other similar studies evaluating driving abilities, it was revealed that patients with dementia performed worse in comparison with their own age groups [59,60]. One of the cognitive tests, MMSE test can be used to evaluate unsafe driver. The American Academy of Neurology states that individuals with an MMSE score of ≤24 may be useful in identifying those at high risk for unsafe driving [58]. In our study, besides the MMSE test, MOCA, QMCI, the forward-backward digit span test, and the clock drawing test were applied to the patients. The MOCA and QMCI tests were shown in our study to correlate with driving skills in different areas of driving assessment. The MMSE test score was above the population average in the patients in our study. MOCA and QMCI tests are relatively more complex than the MMSE test, which is widely used all over the world and whose validity and reliability have been proven many times and also it was shown that the Q-MCI is superior to MMSE and similar with MOCA in distinguishing mild cognitive impairment [14]. The median MMSE of the patients included in our study was found to be 29, and it was found that there was no statistically significant relationship with driving parameters. This is due to the low number of our patients and the high MMSE scores of the patients included in the study. MOCA and QMCI tests, on the other hand, have been shown to predict driving safety better in some areas, if not in all areas. These tests, which are easy to apply, can be used in daily life in terms of widespread context and at least may give an idea about driving safety in patients who drive.

CONCLUSIONS

Driving simulation is a popular and useful method in recent years, as it provides practical applicability and rehabilitation, although it does not replace the actual driving test. In our study, it is shown that driving skills decrease with aging while risky driving increases with aging. QMCI and backward digit span tests, which are very easy to apply in clinical practice, will be useful in patients driving vehicles aged 65 and over with the demonstration of a significant relationship with the total driving score, safe driving, and operational skills. Future studies should focus on real-environment on-the-wheel assessments in terms of providing an assessment of driving in real-life situations. Furthermore, other studies should investigate the minimum required

tests to determine safe driving or risky driver without needing an on-the-wheel test to provide safer assessment environment.

Author contribution

Study conception and design: ME, CB, BBD, OTA, BT MU; data collection: ET, SC, MK, AOB, OA; analysis and interpretation of results: MU, MH, MC ; draft manuscript preparation: ME, OTA. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Hospital Local Ethics Committee (Protocol no. 22/775).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Evaluation of the results of intra-articular platelet-rich plasma injections in patients with knee osteoarthritis

Öznur Uzun
ORCID: 0000-0002-3888-1064

Ankara Bilkent City Hospital, Physical Therapy and Rehabilitation Ankara, Türkiye.

Corresponding Author: Öznur Uzun
E-mail: soznuruzuns@gmail.com

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ABSTRACT

Objective: Osteoarthritis (OA) is the most common form of arthritis, resulting from the degradation of articular cartilage, degradation and proliferative reformation of subchondral bone and a low degree of synovitis that leads to a reduced quality of life. There is no established cure for knee OA. Treatment modalities which have an effect on the underlying biological processes responsible for OA pathogenesis may have potential. One such modality drawing attention is platelet-rich plasma (PRP) injections. In this study, we aimed to evaluate the effects of PRP injections retrospectively in patients with knee OA and the outcomes of two different volume injections.

Materials and Method: A total of 314 patients were included in the study. After baseline physical examination, each patient was evaluated with VAS score and WOMAC before the procedure. All the patients received two intra-articular injections one month apart with autologous PRP and were followed up for a minimum period of 1 year (range, 12-34 months). Two weeks after the injections, the physical examinations of the patients and their evaluations with VAS scores and WOMAC criteria were repeated.

Results: Both VAS scores and WOMAC scores showed significant differences after the first injection ($p<0.05$). Although both scores increased after the second injection, the differences were not significant ($p>0.05$). We also showed that as BMI increased both VAS scores and WOMAC scores increased.

Conclusion: Although our study showed that PRP injections have favorable improvements in the management of knee OA such as reducing the pain and decreasing joint stiffness, PRP injections in the treatment of knee OA needs more standardized research.

Keywords: osteoarthritis, osteoarthritis PRP, PRPVAS, VASknee osteoarthritis, knee osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, resulting from the degradation of articular cartilage, degradation and proliferative reformation of subchondral bone and a low degree of synovitis that leads to a reduced quality of life [1,2]. According to the results of Global Burden of Disease 2010 study, hip and knee OA was ranked as the 11th highest contributor to global disability and 38th highest in disability-adjusted life years [3,4]. Knee OA accounts for approximately 85% of the burden of OA worldwide [5]. The global burden of knee OA is comparable with that of patients with cardiac dysrhythmias, liver cirrhosis or stage IV kidney disease [6]. Moreover, with the aging of the population and increase in obesity throughout the world, it is expected that the burden of OA will become a major problem for healthcare systems globally [2].

There is no established cure for knee OA. Knee OA management strategies include improvement in function, reduction in disability, pain relief and hence, improved quality of life (QoL). Recommended medical therapies like analgesics and anti-inflammatory agents have short-term clinical benefits with small to moderate effect [7]. Intra-articular hyaluronic acid (HA) is controversial with inconsistent recommendations [8]. Intra-articular corticosteroids are generally recommended and their short-term effects were found to be significantly greater than those of intra-articular hyaluronic acid [9]. However, they have short-term pain relief ability [8]. Although arthroplasty is a common and effective procedure for advanced hip or knee OA, there is a risk of serious medical and surgical complications [5]. This is important especially when you take into account the fact that the patients needing surgery are older.

Treatment modalities which have an effect on the underlying biological processes responsible for OA pathogenesis may have potential. One such modality drawing attention is platelet-rich plasma (PRP) injections. PRP is an autologous fraction of human blood and has a greater concentration of platelets than baseline levels of whole blood [10]. PRP functions through platelet degradation products, including multiple growth factors, which have well-defined roles in a range of critical tissue healing processes such as chondrocyte apoptosis inhibition, bone and vessel remodeling, inflammatory modulation and collagen synthesis [11].

In this study, we aimed to evaluate the effects of PRP injections retrospectively in patients with knee OA and the outcomes of two different volume injections.

PATIENTS AND METHODS

The present study was conducted according to the Helsinki Declaration of 1975. All patients signed a written informed consent following a full explanation of the treatment protocol. We recorded patients' demographics and pre-injection data, including age, sex, body mass-index (BMI), visual analogue scale (VAS) pain score and Kellgren-Lawrence classification (Table 1). BMI was calculated as weight in kilograms divided by the square of height in meters. Only the patients between 50-70 years of age who had Kellgren-Lawrence grade 2-3 OA and fulfilling American College of Rheumatology (ACR) criteria of OA were included. Patients were excluded if they had severe OA, glucocorticoid or hyaluronic acid injections in the past 6 months, ongoing anticoagulation therapy.

The primary outcome was the VAS pain score. Secondary outcome includes Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). After baseline physical examination, each patient was evaluated with VAS score and WOMAC before the procedure.

All the patients received two intra-articular injections one month apart with autologous PRP

Table 1. Preinjection demographic findings.

Variables	Unilateral Knee Injection	Bilateral Knee Injection
Male (number of patients)	71	51
Female (number of patients)	65	127
Age (mean)	52.9	57.6
BMI (kg/m^2)	29.2	30.4
Kellgren and Lawrance -II (number of patients)	53	76
Kellgren and Lawrance -III (number of patients)	83	102

Table 2. VAS Scores and WOMAC Scores before and after injections.

Variables	Preinjection	After the First Injection	After the Second Injection
Unilateral Knee Injection			
VAS Score	5.44 (± 2.1)	2.72 (± 0.67)	3.14 (± 1.12)
WOMAC Score	63.93 (± 7.3)	39.67 (± 3.2)	41.72 (± 4.5)
Bilateral Knee Injection			
VAS Score	5.36 (± 2.2)	3.11 ± (0.71)	3.47 ± (1.24)
WOMAC Score	67.41 (± 9.1)	41.52 (± 4.5)	43.25 ± (6.1)

and were followed up for a minimum period of 1 year (range, 12-34 months). Two weeks after the injections, the physical examinations of the patients and their evaluations with VAS scores and WOMAC criteria were repeated (Table 2).

PRP preparation

A peripheral venous blood sample of 15 mL was obtained from the upper extremities of the patients, and 1.5 mL of the sample was used for a platelet count. The remaining 13.5 mL was mixed in a 15-ml sterile centrifuge tube containing 1.5 mL of 3.2% sodium citrate and centrifuged at 1800 rpm for 10 minutes in a centrifuge (Digisystem, New Taipei City, Taiwan). After centrifugation, 6 mL of PRP was obtained from the middle fraction of the blood sample between the erythrocytes and the plasma.

Intra-articular PRP injection

Lateral to patellar tendon, a 25-gauge needle was slowly inserted into inferior lateral aspect of the patella at a 45-degree angle with the knee flexed to 90 degrees. The injection was stopped if the patient experienced pain or a sensation of pins and needles. For unilateral knee OA, 5 ml PRP was administered. For bilateral knee OA, 3 mL of PRP was administered into each knee joint. The patient was discharged after the injection. Limited movement was allowed in the knee for 24 hours, and resting was recommended in the case of pain. Non-steroidal inflammatory drug use was restricted in both groups because of the possibility of platelet function inhibition. Intermittent icepack compression was recommended to relieve discomfort in the knee.

Statistical analysis

The data were analyzed using SPSS version 23.0 (IBM statistics for Windows version 23, IBM Corporation, New York, NY). A Shapiro-Wilk test revealed that VAS scores and WOMAC scores were normally distributed. Paired sample t-tests were used to examine changes within the groups. Pearson's correlation test and Spearman's rho test were used to determine whether any correlation existed between variables. Quantitative variables were indicated as mean and standard deviation (±). The results were considered statistically significant when the p-value was < 0.05.

RESULTS

A total of 314 patients were included in the study. Of them, 192 was female, 122 was male. 178 patients had bilateral knee OA injections at the same time. The remaining patients had unilateral injections.

Both VAS scores and WOMAC scores showed significant differences after the first injection ($p<0.05$). Although both scores increased after the second injection, the differences were not significant ($p>0.05$).

The mean platelet count of the PRP was 1.681×10^6 ($\pm 3.53 \times 10^5$) and that of whole blood was 2.41×10^5 ($\pm 4.67 \times 10^4$). We were not able to show a significant correlation between the mean platelet count in the PRP and outcomes (Pearson's correlation coefficient $r = 0.192$). The mean BMI was 29.8 kg/m^2 (±4.15). On the other hand, as BMI increased both VAS scores and WOMAC scores increased. (Pearson's correlation coefficient $r = 0.872$).

DISCUSSION

Our study demonstrated that PRP injections into the knee joint in patients with mild to moderate knee OA proved to be effective in reducing pain, as shown by the improvement in the VAS scores 3 months after the injections. This could be due to the immediate and sustained release of growth

factors over a prolonged period, which enhances healing resulting in sustained clinical effects [12]. Nevertheless, we believe that PRP has modulatory effects on synovial cavity that cannot be explained merely by the effects of the one specific growth factor that it contains. PRP use has been advocated as a treatment option in all stages of knee OA [1]. Intra-articular PRP injections in patients with knee OA show significant improvements in pain reduction, improved symptoms and QoL [13,14].

The ideal PRP volume has not been studied enough yet. Most of the studies have focused on the number of platelets in PRP rather than its volume, or how often to apply it. Spakova et al., [15] and Paterson et al., [16] have used 3 ml PRP whereas Patel et al., [17] and Sanchez et al., [18] have used 8 ml PRP. Our previous clinical experience was that PRP injections of more than 6 ml were found to be uncomfortable by patients because they were painful.

There have been lots of randomized controlled trials in knee OA mostly comparing PRP to intra-articular injection of HA. All studies are of low to moderate methodological quality and use variable PRP protocols. In general, results showed that PRP is a safe treatment with potential to provide symptomatic benefit for OA at least in the short term. The enhanced effectiveness of PRP for pain treatment and knee joint function in comparison to HA or placebo and positive outcomes in all stages of knee OA have all been reported [19-21]. It has also been shown in a few in vitro as well as clinical studies that combination of PRP with HA may exert a synergistic effect [22].

In knee OA, PRP injections aim to stimulate cartilage repair and offer relief to other osteoarthritic symptoms, potentially delaying the need for joint replacement surgery. PRP injections have shown to influence the entire joint environment, leading to a short-term clinical improvement [23]. Recently a randomized clinical trial has shown that knee injections of PRP did not significantly improve knee pain or reduce medial tibial cartilage volume loss at 12-month follow-up, compared with placebo saline injections, in people with symptomatic mild to moderate radiographic knee OA [24]. However, Lin et al showed that intra-articular injection of PRP can significantly reduce the subchondral bone marrow edema and the level of biomarkers in synovial fluid of the symptomatic knee osteoarthritis [25].

Intra-articular glucocorticoid injections are efficacious for short-term pain relief, commonly lasting a few weeks, and may be a useful adjunct therapy, particularly for an upcoming life event [26]. Regular injections are not recommended; in patients with symptomatic knee OA, 2 years of treatment with triamcinolone, administered intra-articularly every 3 months, resulted in greater loss of cartilage volume than saline injections [27].

There are many controversies with regard to the best volume and formulation of PRP, the number and frequency of injections, the need for ultrasound guidance, the speed and duration of spins to isolate the PRP, whether an activating agent is necessary and co-administration with a local anesthetic. The variety of PRP application process, including PRP collection volumes and preparation protocols, reflects an absence of consistency among trials. Cell membrane receptors are limited, so very high concentrations of growth factors probably have no beneficial effect on cell stimulatory processes [28]. Different preparation methods are known to yield different PRP product in the same donor [29]. Intra-individual variation in the PRP product with the same technique at different time frames is also noted [30]. The ideal PRP needed for treatment of knee OA is not clearly defined and requires further standardization [22].

The ACR strongly recommends weight loss and exercise as non-pharmacological cures for knee OA. Oral and topical non-steroidal anti-inflammatory drugs and intra-articular glucocorticoid injections are strongly recommended, whereas there is no recommendation about PRP injections [31]. In a recent randomized clinical trial, intra-articular injection of PRP, compared with injection of saline placebo, did not result in a significant difference in symptoms or joint structure at 12 months among patients with symptomatic mild to moderate radiographic knee OA 24. Although the authors reported that that the PRP preparation used in their study contained elevated concentrations of growth factors and cytokines that promote tissue healing and inhibit inflammatory processes, we strongly believe that it is not the concentration that shows the benefit, but the effect of the content.

High BMI or BMI ≥25 kg/m^2 is one of the most critical risk factors of OA and needs to be included in global- and national-level prevention policies. The increasing prevalence of overweight and obesity is

contributing to the increasing burden of OA [32]. Consistent with this fact, the study population consisted of a large proportion of overweight patients. We also found that PRP application was less effective in obese patients in our study.

Although our study showed that PRP injections have favorable improvements in the management of knee OA such as reducing the pain and decreasing joint stiffness, PRP injections in the treatment of knee OA needs more standardized research. Stronger medical evidence is required, because of confusing literature.

Author contribution

Study conception and design: ÖU; data collection: ÖU; analysis and interpretation of results: ÖU; draft manuscript preparation: ÖU. The author reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ankara Bilkent City Hospital Clinical Research Ethics Committee (Protocol no. E2-22-2001 / 22.06.2022).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Low-grade glial tumors: The experience of an oncology hospital in Türkiye*

Serdar Ceylan[1]
ORCID: 0000-0001-5885-4023

Neyran Kertmen[2]
ORCID: 0000-0001-7654-5822

Gözde Yazıcı[3]
ORCID: 0000-0002-7430-6729

Ayşe Kars[2]
ORCID: 0000-0002-7964-9835

[1] Hacettepe University, Faculty of Medicine, Department of Internal Medicine, Ankara, Türkiye.

[2] Hacettepe University, Cancer Institute, Division of Medical Oncology, Ankara, Türkiye.

[3] Hacettepe University, Faculty of Medicine, Department of Radiation Oncology, Ankara, Türkiye.

* The study has been presented at 3. International and 7. Medicine and Treatment Congress.

Corresponding Author: Serdar Ceylan
E-mail: serdar.ceylan@hacettepe.edu.tr

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ABSTRACT

Objective: Several factors are important in the prognosis of low grade gliomas, besides genetic changes. The present study aims to examine the effect of other factors on prognosis except for genetic changes in low grade gliomas (LGGs).

Materials and Methods: Patients diagnosed with "brain malignant neoplasm" who were referred to Hacettepe University Oncology Hospital were screened. Among these patients, 148 patients with a supratentorial low grade gliomas whose data are completely available were included. Patients were followed for at least five years after diagnosis or death within this period.

Results: Mean age of diagnosis was 36.2±10.7 years, and 52.7% of patients (n=78) were females, Most common subtype was oligodendroglioma (n=86, 58.1%). Sixty-two of patients relapsed (41.9%). The 5-year mortality rate was 35.1% (n=52). Kaplan-Meier analysis of the variables, the only difference was between histopathological subtypes (p=0.03). Astrocytoma histology was related to wporse prognosis. Cox regression analysis of factors affecting 5-year mortality, advancing age (HR: 1.03, 95% CI: 1.00-1.06, p=0.03), astrocytoma (HR: 2.59, 95% CI: 1.35-4.98, p=0.004) and oligoastrocytoma (HR: 2.13, 95% CI: 1.02-4.43, p=0.04) were identified to increase the mortality risk.

Conclusion: The age of the patients and the histopathologic subtype of the tumor must be taken into consideration during the follow-up and treatment of low grade gliomas.

Keywords: astrocytoma, glioma, mortality, survival.

INTRODUCTION

Central nervous system tumors are defined according to the type of cell they originate from and the histopathological characteristics of these cells. Gliomas are neuroepithelial tumors arising from glial cells. According to the 2007 WHO classification system, low-grade gliomas (LGGs) are grade I and II tumors [1]. Low-grade gliomas constitute approximately 5% of all primary brain tumors and 15% of all glial tumors [2,3]. They are rare tumors that are more common in the young population [4]. In the diagnosis of LGGs, after it is determined that there may be LGG according to the radiological features of mass by radiological methods, surgical resection or biopsy is performed. Afterward, diagnosis is confirmed by examination for histopathological and molecular changes [5].

Mutations/deletions in various genes are of great importance in the course of the disease [6]. Size, location and histopathological type of tumor, tumor crossing the midline, neurological deficits before surgery, patient's age, and performance status are important in the prognosis of LGGs, besides genetic changes [7,8]. In LGGs, the average life expectancy is shorter than ten years from the time of diagnosis. Median overall survival can be extended to over ten years with aggressive treatment [9].

Low-grade gliomas have been studied primarily in retrospective studies. Data on LGG are also from highly developed countries. [4]. Limited data are available from low- and middle-income countries. The present study serves up information from a middle-income, developing country and aims to examine the effect of other factors on prognosis except for genetic changes in LGGs retrospectively. Molecular study results were not included in the present study, since changes at the molecular level in pathology samples have been understudied.

MATERIAL AND METHODS

Participants

Four thousand nine hundred ninety-one patients diagnosed with "brain malignant neoplasm" who admitted to Hacettepe University Oncology Hospital between 01.01.2008 - 01.01.2017 were screened through the hospital automation recording system. Among these patients, 148 patients with a supratentorial LGG whose data are completely available were included in the study.

Study Protocol

Demographic and clinical data were obtained from the hospital automation recording system. Age of diagnosis, gender, localization of the tumor, crossing the midline, if the surgery was performed, the pathological examination results, presence of primary/adjuvant treatment, relapse situation, and 5-year survival were obtained. During the follow-up period, it was accepted as relapse if the tumor progressed. Patients were followed for at least 5 years after diagnosis if there was no exitus. The exitus status of patients was obtained from the death notification system.

Statistical Analysis

Descriptive statistics were used to show the characteristics of patients. Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as mean and standard deviation or median and interquartile range values according to the normal distribution. Kaplan-Meier was performed for survival analysis. The Log-Rank test was used for comparative analysis of survival rates. Cox regression analysis was applied for examining the factors that affect the 5-year survival rate independently. Variables with a p-value of <0.20 were added to the regression model, and variables that were expected to affect survival rate even if the p-value was not <0.20. In all statistical comparisons, the p-value for significance was accepted as <0.05. Statistical Package for the Social Sciences (SPSS) 24.0 (Armonk, NY: IBM Corp.) was wielded for statistical analysis.

RESULTS

The mean age of diagnosis was 35.0 (Interquartlile range: 30.0-43.5) years, and the number of patients 40 years and over at diagnosis was 56 (37.8%). Fifty-two point seven percent of patients (n=78) were females, 43.9% (n=65) of the tumors were located in the frontal lobe, 14.9% (n=22) in the temporal lobe, 6.1% (n=9) in the parietal lobe, and 35.1% (n=52) in more than one lobe. In 96 patients

information about midline status of the tumor could be obtained, of these 16 (16.7%) had tumors crossing the midline. One hundred thirty-nine (93.9%) patients were operated. On histopathologic examination, most of the tumors were grade II (n=140, 94.6%) therefore we are dealing with mainly grade II tumors in this study. The most common subtype was oligodendroglioma (n=86, 58.1%) and the least oligoastrocytoma(n=23, 15.5%). The number of patients who received primary/adjuvant treatment was 97 (65.5%). Radiotheraphy (RT) was given to everyone who received primary/adjuvant treatment, while chemotheraphy (CT) was given to ten (6.8%) people. Sixty-two of patients relapsed (41.9%). While 40 (64.5%) of them were treated with RT, 45 (72.6%) of them received CT. The 5-year mortality rate was 35.1% (n=52) (Table 1).

The Kaplan-Meier analysis of the variables such as age, gender, localization, crossing the midline, surgery, primary/adjuvant treatment, and relapse status did not show any statistically difference on 5-year mortality rates (Table 2). The only difference was between histopathological subtypes (p=0.03). The 5-year mortality rate for oligodendroglioma was 25.6%, 48.7% for astrocytoma and 47.8% for oligoastrocytoma (Table 2, Figure 1).

Cox regression analysis of factors affecting 5-year mortality, advancing age (HR: 1.03, 95% CI: 1.004-1.066, p=0.03), astrocytoma (HR: 2.59, 95% CI: 1.35-4.98, p=0.004) and oligoastrocytoma (HR: 2.13, 95% CI: 1.02-4.43, p=0.04) were identified to increase the mortality risk. Gender, primary/Adjuvant treatment and relapse status did not have an effect on 5-year mortality (Table 3).

Table 1. Demographic and clinical characteristics of patients.

	N=148 (n, %)
Age of Diagnosis (years) (median, interquartile range)	35.0 (30.0-43.5)
≥40 years	56 (37.8)
Gender (female)	78 (52.7)
Lobe	
Frontal	65 (43.9)
Temporal	22 (14.9)
Parietal	9 (6.1)
≥2 lobes	52 (35.1)
Crossing the Midline (n=96)	16 (16.7)
Surgery	139 (93.9)
Histopathological Examination	
Grade	
I	4 (2.7)
II	140 (94.6)
Undetermined	4 (2.7)
Subtype	
Oligodendroglioma	86 (58.1)
Astrocytoma	39 (26.4)
Oligoastrocytoma	23 (15.5)
Primary/Adjuvant Treatment	97 (65.5)
Radiotheraphy	97 (65.5)
Chemotheraphy	10 (6.8)
Relapse	62 (41.9)
Treatment After Relapse	
Radiotheraphy	40 (64.5)
Chemotheraphy	45 (72.6)
Exitus	52 (35.1)

Table 2. Demographic and clinical characteristics of patients.

	Deaths (N,%)	P*
Age of Diagnosis (years)		0.89
<40	32 (34.8)	
≥40	20 (35.7)	
Gender		0.95
Female	28 (35.9)	
Male	24 (34.3)	
Localization		0.32
Frontal	27 (41.5)	
Temporal	6 (27.3)	
Parietal	1 (11.1)	
≥2 lobes	18 (34.6)	
Crossing the Midline (n=96)		0.59
Present	32 (40.0)	
Absent	7 (43.8)	
Surgery		0.57
Present	48 (34.5)	
Absent	4 (44.4)	
Subtype		0.03
Oligodendroglioma	22 (25.6)	
Astrocytoma	19 (48.7)	
Oligoastrocytoma	11 (47.8)	
Primary/Adjuvant Treatment		0.33
Present	15 (29.4)	
Absent	37 (38.1)	
Relapse		0.37
Present	32 (37.2)	
Absent	20 (32.3)	

*Results from Kaplan-Meier survival analysis

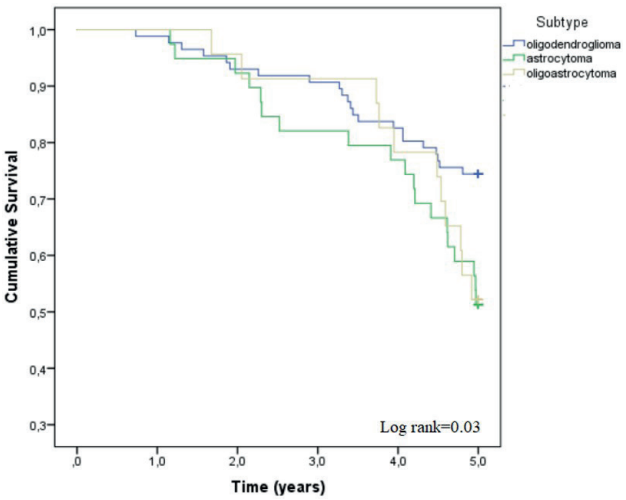

Figure 1. Histological subtypes and 5-year mortality.

Table 3. Multivariate regression analysis of factors affecting 5-year mortality rate.

	HR	95% CI	P
Age of Diagnosis (years)	1.03	1.004-1.066	0.03
Gender (female)	1.01	0.58-1.76	0.96
Subtype			0.01
Oligodendroglioma	Ref	Ref	
Astrocytoma	2.59	1.35-4.98	0.004
Oligoastrocytoma	2.13	1.02-4.43	0.04
Primary/Adjuvant Treatment	1.03	0.54-1.97	0.92
Relapse	0.86	0.48-1.52	0.60

HR: Hazard ratio, CI: Confidence Interval

DISCUSSION

Low-grade gliomas are a rare group of the primary brain tumors. A new classification was made by World Health Organization in 2016 [10] and updated in 2021 [11], but many features from the old classification are similar to the new version. Retrospective follow-up data of 148 patients with LGGs were analyzed in the present study and the results suggest that age and histopathological subtype were related to 5-year mortality rate.

Patients diagnosed with LGG are usually diagnosed at a young age, and the average age at diagnosis is in the range of 35-40 years [12]. In the present study, the mean age at diagnosis was 36.2±10.7, in line with data in other studies. The young age at diagnosis complicates treatment because it involves patients who are fertile and when the tumor is an eloquent area, applying a standardized algorithm becomes more difficult.

The prognosis of LGGs has not improved over the years, despite improved diagnosis and treatment methods. Treatment decisions are generally made according to clinical variables although considerable advances are made at molecular-level [13]. The median survival of LGG patients is between 4.7 and 9.8 years [14]. Overall survival decreases with increasing age at diagnosis [15]. The Pignatti risk score takes age 40 as a threshold and considers age 40 and over as high risk [16]. In addition, in recent studies it is stated that the age limit, which indicates a poor prognosis, is higher [17-19]. Reasons for this are reduced performance score with increasing age, increased frequency of comorbidities, an increase in tumor diameter, and inability to achieve total resection [20]. In the present study, advancing age at the diagnosis was found as a risk factor for 5-year mortality.

Astrocytomas constitute the most common LGG histology [4,21], but in our series oligodendrogliomas were more frequent and astrocytomas were the second. Astrocytoma histology indicates worse prognosis. Pignatti risk score also includes astrocytoma histology [16]. In the North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study, oligodendroglioma or oligo-dominant histology has better survival rates. Histologic subtype and age combined, were particularly powerful indicators of overall survival [22]. In the present study, astrocytoma histology is associated with lower survival rates and the combination of age and histology shows a strong relationship with survival similar to literature.

Early maximum tumor resection within safe limits is the standard treatment in LGG management [23,24]. With early resection, uncertainty in the radiological diagnosis is eliminated, and malignant transformation is delayed, and as a result, survival is increased [24]. Studies comparing follow-up after biopsy with early resection report longer survival with the latter mode [25,26]. On the other hand, there are also contradictory data that early resection does not affect survival compared to the wait-and-

see strategy. By delaying surgical intervention, the patient spends a longer time without impairment in the quality of life [27]. Surgical treatment was not found to have a significant effect on the 5-year mortality rate and there is no satisfactory data on quality of life in the present study. Some studies also indicate that adjuvant therapy does not improve survival [4]. Similar results were found for primary/adjuvant treatment on the 5-year mortality rate in the present study.

Relapse is a significant issue in the follow-up and treatment of these tumors. Patients with low-risk scores are generally followed up without treatment after surgery; high-risk patients receive adjuvant RT and/or CT after surgery. Despite these treatments relapses occur [13,28,29]. In the present study, relapse rate was 41.9% in five years and relapse status did not affect the 5-year mortality rate. This could be because the follow-up was limited to five years.

Some limitations exist due to the retrospective nature of the study. Since patients were lost to follow up for various reasons, data of some patients could not be reached. As studies at the molecular level were not done regularly in the past, data on this subject remained limited. Therefore, molecular study results were not included in the present study. High-grade tumors may have been misdiagnosed due to the possibility of heterogeneity in tumors that underwent subtotal resection and were diagnosed by biopsy. In LGGs, classification of tumors at pathological examination can be difficult, and low level of interobserver concordance may complicate the diagnostic approach further [30]. Because the follow-up period was limited to 5 years, the negative effects of relapse may not have been observed. The present study does not contain information on performance status, quality of life, and toxicity. Another limitation is that the causes of death are unknown. Since the patients were young, their accompanying chronic diseases were few, they were not included in the analysis.

CONCLUSION

Despite the advances in diagnosis, the characteristics of the patients and the histopathological features of the tumor remain to be important. The age of the patients and the subtype of the tumor must be taken into consideration during the follow-up and treatment of the patient.

Author contribution

Study concept adn design: S.C., A.K.; Supervision: N.K., G.Y.; Data collection and interpretation of results: S.C., A.K.; Literature search: S.C., A.K.; Writing: S.C., A.K.; Critical review: N.K, G.Y. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Non-Interventional Clinical Researches Ethics Board (Protocol no. 17/771-07).

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Conflict of interest

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acta medica

CASE REPORT

T-wave oversensing and symptomatic bradycardia in a pacemaker-dependent heart failure patient due to drug-induced hyperkalemia

Samuray Zekeriyeyev[1]
ORCID: 0000-0001-7458-3956

Ugur Canpolat[1]
ORCID: 0000-0002-4250-1706

Kudret Aytemir[1]
ORCID: 0000-0001-9279-8424

[1] Hacettepe University Faculty of Medicine, Department of Cardiology, Ankara, Türkiye.

Corresponding Author: Ugur Canpolat
E-mail: dru_canpolat@yahoo.com

ABSTRACT

Hyperkalemia is a common clinical condition among heart failure patients especially if there is coexisting older age, potassium-sparing medication, and renal insufficiency. Close follow-up and titration of renin-angiotensin-aldosterone system inhibitors are essential to prevent the development of hyperkalemia. It can also cause significant abnormalities in patients with cardiac implantable electronic devices (CIED) including pacemakers and implantable cardioverter defibrillators (ICD) due to its impact on cardiac electrophysiology. Herein, we presented a pacemaker-dependent heart failure patient with single-chamber ICD in whom bradyarrhythmia signs and symptoms were observed due to T-wave oversensing and managed appropriately.

Keywords: heart failure, hyperkalemia, t-wave oversensing, bradycardia.

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INTRODUCTION

In clinical practice, hyperkalemia is a common electrolyte abnormality particularly among elderly heart failure patients (with potassium-sparing medications) if there is coexistent acute/chronic renal failure 1. In patients with a cardiac implantable electronic device (CIED), hyperkalemia causes significant changes including widening of the paced QRS complex, increased atrial and ventricular pacing thresholds causing failure to capture, increased latency (usually with ventricular pacing) presented by a delay of the interval from the pacemaker stimulus to the onset of QRS, and oversensing of paced or spontaneous tall T waves causing inappropriate implantable cardioverter-defibrillator (ICD) shocks 2. Herein, we presented a pacemaker-dependent heart failure patient who was admitted with dizziness, weakness, and bradycardia despite the basal rate of pacing being set at 60 bpm in whom hyperkalemia induced T wave oversensing and delay in ventricular pacing were diagnosed and managed appropriately.

CASE

A 79-year-old male patient with a history of cardiac resynchronization therapy defibrillator (CRT-D) implantation after an atrioventricular (AV) node ablation due to ischemic cardiomyopathy and drug-resistant AF with high ventricular rates was admitted to our clinic due to CIED infection. After complete extraction of the infected left-sided device including all leads and battery, the patient was followed up with a temporary transvenous pacemaker for 3 weeks under i.v. antibacterial therapy. After 3 weeks, the patient underwent right-sided VVİ-ICD implantation. The basal rate of the VVI-ICD was set to 60 bpm. During in-hospital follow-up, the patient was closely monitored and the heart rate was observed as 60 bpm at the electrocardiography (ECG). He has been discharged uneventfully with optimal medical therapy for heart failure and atrial fibrillation. His final medical therapy included rivaroxaban (15 mg o.d), carvedilol (12,5 mg b.i.d), candesartan (8 mg o.d), furosemide (40 mg o.d), and spironolactone (25 mg o.d). At the

time of discharge, serum potassium level was 3.66 mEq/L, and serum creatinine level was 1.13 mg/dL.

During the first week's follow-up visit, he complained of intermittent dizziness and the laboratory tests showed a serum potassium level of 5.42 mEq/L, and a serum creatinine level of 1.85 mg/dL. The 12-lead ECG revealed a ventricular paced rhythm with a rate of 60 bpm (Figure 1). Pacemaker interrogation revealed no abnormality at baseline parameters, pacing, and sensing measures. Thus, candesartan 8 mg o.d and spironolactone 25 mg o.d was stopped due to impaired renal functions and increased potassium level and a 24-hour Holter monitorization was planned for his intermittent dizziness. However, his dizziness frequency was increased and weakness in the upper and lower extremities was developed during follow-up. 24-hour Holter monitorization showed intermittent bradycardia episodes (ventricular rate of 40 bpm) during his symptoms (Figure 2A). Therefore, he was hospitalized for further follow-up. It was learned that the patient continued to use candesartan 8 mg o.d and spironolactone 25 mg o.d. The 12-lead ECG showed an intermittent bradycardia episode with a ventricular pace rate of 40 bpm despite the pacemaker basal rate setting being 60 bpm (Figure 2B). No abnormal pacing spikes or capture failure was observed. Laboratory tests showed a serum potassium level of 6.96 mEq/L, and a serum creatinine level of 2.08 mg/dL. After ICD interrogation, intermittent T-wave oversensing was observed causing a ventricular rate of 40 bpm and it was eliminated by changing the sensing polarity. Intravenous insulin, inhaled beta-agonists, and intravenous calcium gluconate were administered for hyperkalemia management. All nephrotoxic medications were stopped during the hospitalization period because of acute renal failure and hyperkalemia. His symptoms, ECG recording, and T-wave oversensing were improved after normalization of serum potassium and creatinine levels and discharged uneventfully.

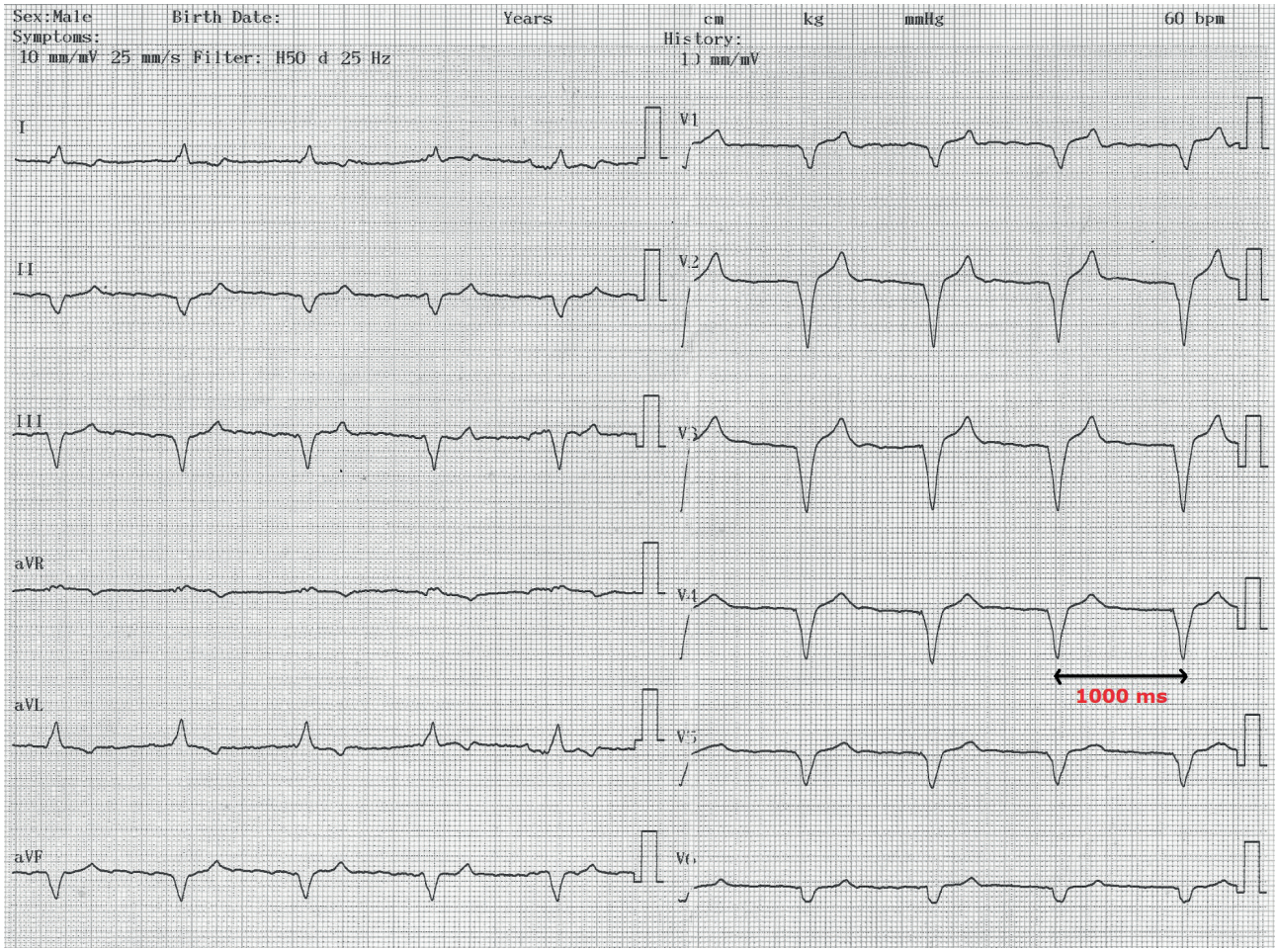

Figure 1. The 12-lead ECG revealed a ventricular-paced rhythm with a rate of 60 bpm

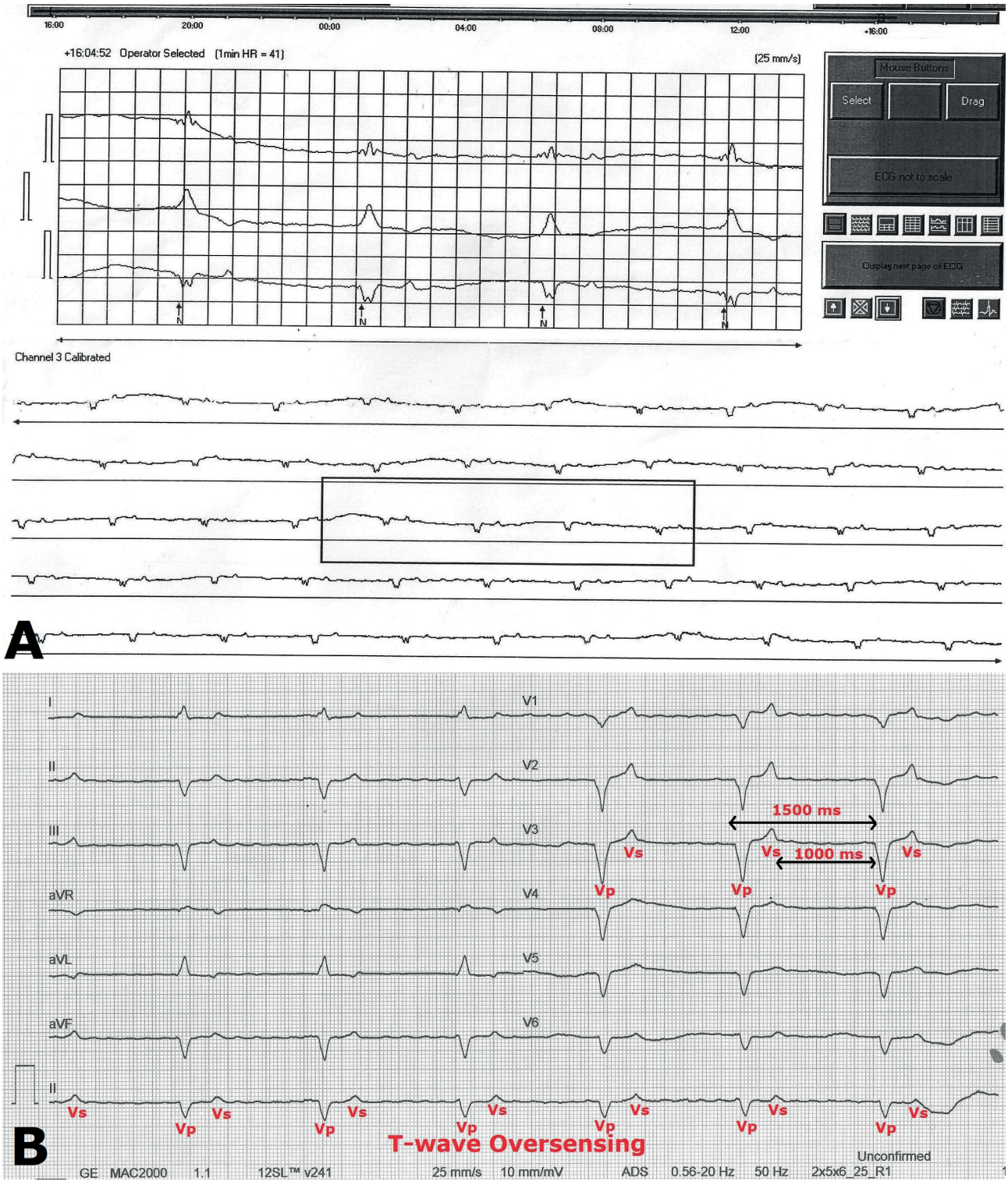

Figure 2. A) A 24-hour Holter monitorization showed intermittent bradycardia episodes (ventricular pacing rate of 40 bpm) during his symptoms. B) The 12-lead ECG showed an intermittent bradycardia episode with a ventricular pace rate of 40 bpm despite the pacemaker basal rate setting being 60 bpm

DISCUSSION

Hyperkalemia is a common clinical problem that is most often a result of impaired urinary potassium excretion due to acute or chronic kidney disease (CKD) and/or systemic disorders or drugs inhibiting the renin-angiotensin-aldosterone system (RAAS). Daily clinical practice shows that it is common among elderly patients undergoing optimized heart failure treatment (with potassium-sparing drugs)

especially if there is coexisting renal insufficiency 2. In the TREAT HF (Turkish Research Team-Heart Failure) study, its prevalence has been reported as 17.7% among patients with heart failure and chronic renal disease 3. The most serious manifestations of hyperkalemia are muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias. These manifestations usually occur when the serum potassium concentration is ≥7.0 mEq/L with chronic hyperkalemia or possibly at lower levels with an acute rise in serum potassium 1. Hyperkalemia may be associated with a variety of changes on the ECG. Tall peaked T waves with a shortened QT interval are usually the first findings. As the hyperkalemia gets more severe, there is a progressive lengthening of the PR interval and QRS duration, the P wave may disappear, and ultimately the QRS widens further to a sine wave pattern 4. Hyperkalaemia is the most common electrolyte abnormality causing loss of pacing capture. In patients with a CIED, hyperkalemia causes the widening of the paced QRS complex (and paced P-wave if it is seen) because of delayed myocardial conduction, and increased atrial and/or ventricular pacing thresholds causing failure to capture, and oversensing of the peaked T-waves causing inappropriate ICD shocks 2. Although we managed our patient per the current heart failure guidelines regarding optimal medications and close follow-up for electrolyte and renal functions, reminded our patient to stop RAAS inhibitors accordingly, hyperkalemia with significant signs and symptoms was developed because of the continuation of RAAS inhibitors by the patient. It is well known that ICD leads were more sensitive to intracardiac signals than conventional pacemaker leads. T-wave oversensing due to hyperkalemia caused a delay in subsequent ventricular pacing as the patient was pacemaker dependent and the ventricular rate was dropped to 40 bpm in our patient. It was managed by changing the sensing polarity in the acute management and improved after appropriate treatment of hyperkalemia.

In conclusion, hyperkalemia induced by optimal heart failure medications is an important clinical condition that should be suspected, diagnosed, and managed appropriately. It can also cause significant changes in patients with CIEDs including pacemakers or ICDs. Device interrogation and prolonged rhythm monitorization with 24-hour Holter ECG are essential in pacemaker-dependent patients with bradycardia (pacing rate is slower than basal rate setting of pacemaker) and secondary causes like hyperkalemia should be suspected in the absence of primary pacemaker abnormality.

Author contribution

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

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Conflict of interest

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CASE REPORT

Unilateral hyperkeratotic dark plaques covering the entire right lower extremity: A rare entity

Ecem Bostan[1]
ORCID: 0000-0002-8296-4836

Basak Yalici-Armagan[2]
ORCID: 0000-0001-9745-1331

Beril Yel[2]
ORCID: 0000-0002-8863-1311

Ozay Gokoz[3]
ORCID: 0000-0001-9537-1127

[1]Cihanbeyli State Hospital, Dermatology and Venereology Clinic, Konya, Türkiye.

[2]Department of Dermatology and Venereology, Hacettepe University, Faculty of Medicine, Ankara, Türkiye.

[3]Department of Pathology, Hacettepe University, Faculty of Medicine, Ankara, Türkiye.

Corresponding Author: Ecem Bostan
E-mail: bostanecem@gmail.com

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ABSTRACT

Verrucous venocapillary malformation, formerly known as verrucous hemangioma, presents itself as single or multiple, well-demarcated, erythematous plaques that eventually acquire hyperkeratinization, oozing, bleeding and become thicker and darker over time. We report a case of verrucous venocapillary malformation in 33-year old woman referred to the dermatology outpatient clinic with the complaint of hyperkeratotic plaques covering the entire right leg and thigh, present since birth.

Keywords: diagnosis, differential, pathology, vascular malformations.

INTRODUCTION

Verrucous venocapillary malformation (VVM), formerly known as verrucous hemangioma, is characterized by well-demarcated, single or multiple, dark red/purple or black verrucous plaques and nodules which may show hyperkeratinization, thickening, darkening and bleeding [1,2]. VVM usually appears at birth or during early childhood [2]. On the other hand, angiokeratomas are well-demarcated vascular lesions which are characterized histopathologically by superficial vascular ectasia accompanied by hyperkeratosis [3]. Some clinical variants of angiokeratomas include solitary or multiple angiokeratomas, angiokeratoma of the vulva and scrotum, angiokeratoma corporis diffusum (ACD), angikeratoma circumscriptum neviforme (ACN) [3]. Apart from the other types of angiokeratomas, ACN is the only congenital variant of all angiokeratomas [3]. Additionally, ACN is not associated with any inborn errors of metabolism of lysosomal storage, typically Fabry's disease [3]. ACN generally appears at birth or during early childhood and typically manifests itself in the form of hyperkeratotic, violaceous, verrucous plaques just like VVM [4]. Therefore, it is quite essential to differentiate VVM from ACN and histopathological examination is the gold standard for the prompt diagnosis [4]. We report the clinical case of a 33-year old woman referred to the dermatology outpatient clinic with the complaint of dark purple/black hyperkeratotic plaques covering the entire right leg and thigh, present since birth.

CASE PRESENTATION

A 33-year old woman referred to the dermatology outpatient clinic with the complaint of noncompressible, dark purple/black hyperkeratotic plaques covering the entire right leg and thigh. The lesions were present since birth; gradually enlarged and transformed into nontender, verrucous nodules. Magnetic resonance imaging was performed in another institution and revealed the presence of exophytic lesions with deeper subcutaneous and soft tissue involvement on the right extremity, suggestive of VVM. However, no histopathological examination was performed. Our differential diagnoses include verrucous venocapillary malformation, angiokeratoma circumscriptum neviforme (ACN) and glomuvenous malformation. Dermatological examination revealed purpuric-black, discrete/confluent, hyperkeratotic plaques and nodules with variable sizes covering the entire medial right lower limb (Figure 1). There was no mucosal involvement. Histopathological examination showed epidermal hyperkeratosis and elongation of the rete ridges. In the papillary dermis, ectatic small vessels which were surrounded by the elongated rete ridges, were observed (Figure 2A-B). Serial sections revealed malformed vascular proliferations in the subcutaneous tissue and deep dermis was spared (Figure 3A-B). Vacuolization of endothelial cells or lipid inclusions were not present. Since the subcutaneous tissue involvement was apparent, she was diagnosed with VVM with the help of clinical, radiological and histopathological findings. She was referred to plastic and reconstructive surgery department for the excision and split-thickness skin grafting of the large plaques and nodules.

DISCUSSION

VVM, also known as verrucous hemangioma, is a rare congenital vascular malformation which is usually localized to the lower extremity, unilaterally [2]. Even though, VVM has an immune profile analogous to the vascular proliferations; it exhibits histopathological features, clinical behavior and evolution pattern of vascular malformations [2,3]. VVM is present at birth or appears during early childhood, in the form unilateral, localized or grouped, erythematous patches which eventually transform into hyperkeratotic, confluent, dark

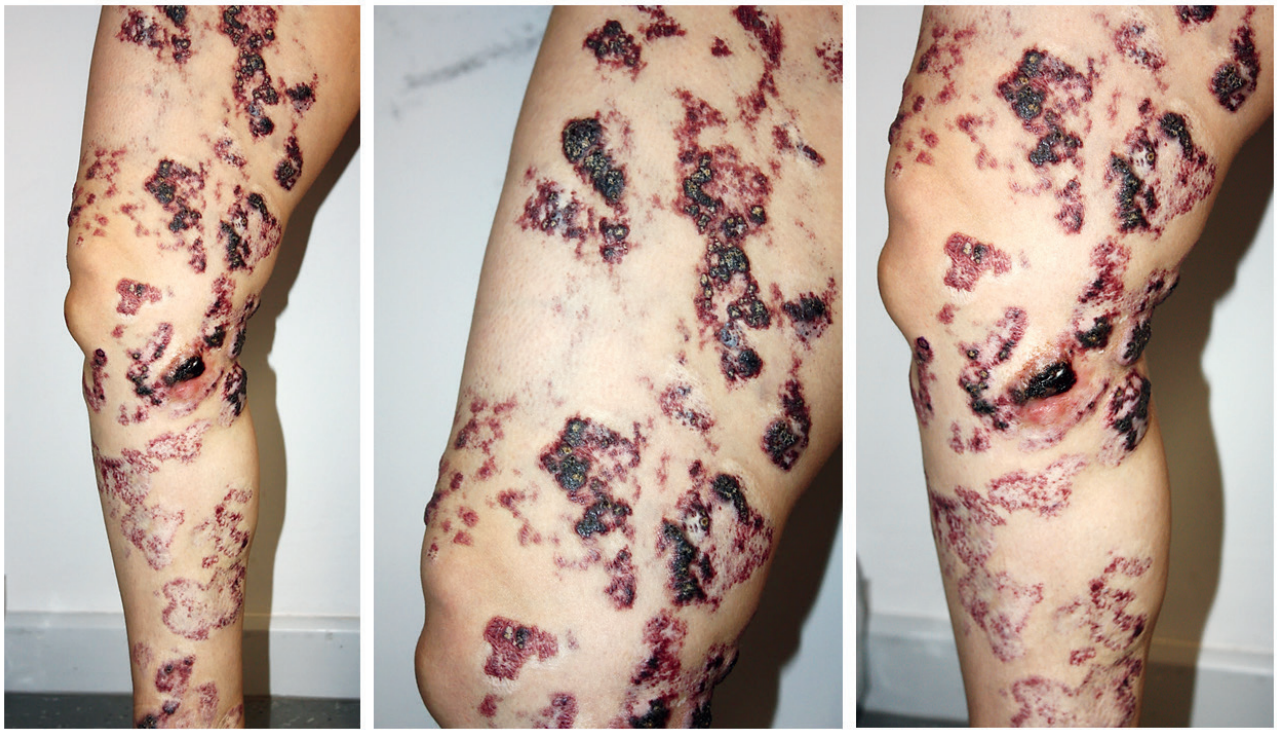

Figure 1. Multiple, violaceous to black, verrucous plaques and nodules of variables sizes accompanied by hyperkeratinization are present on the entire right thigh and leg. Some plaques on the right leg were excised and skin grafting was applied.

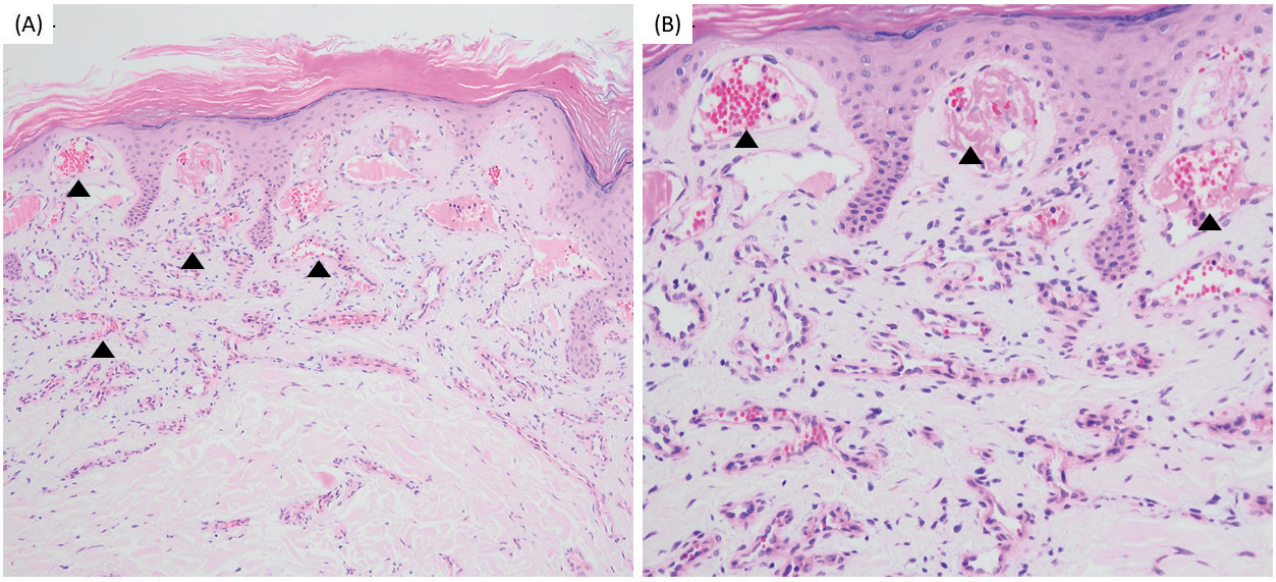

Figure 2. Hyperkeratosis with irregular acanthosis in the epidermis. Dilated vascular channels in between elongated rete ridges in the papillary dermis (arrowheads) (A), (H.E x100). Dilated capillaries some filled with fibrinous thrombus (arrowheads) (B), (H.E. x200).

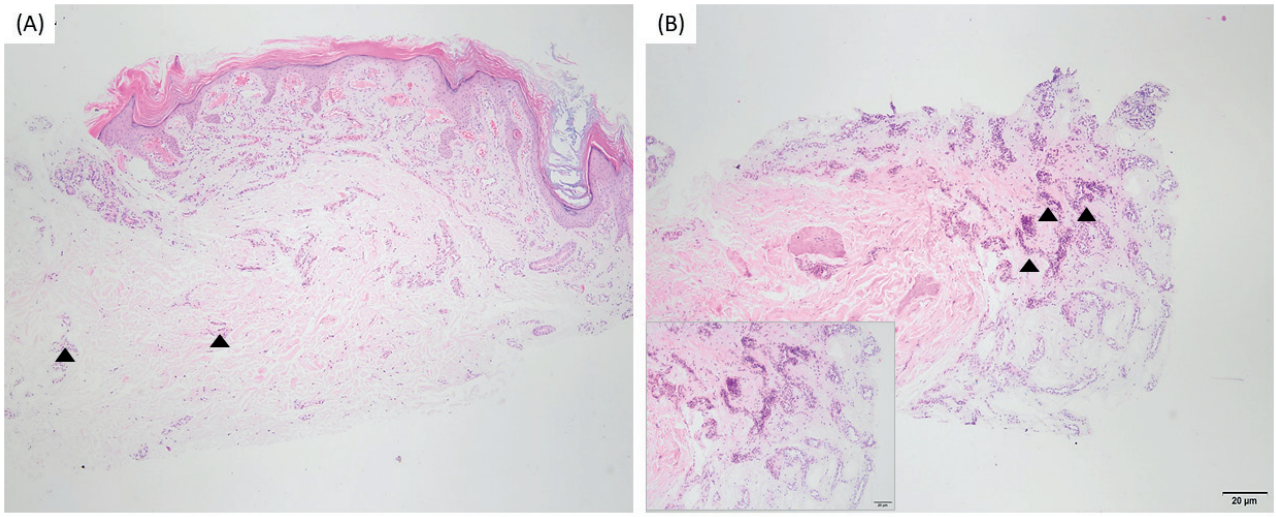

Figure 3. Although mid and deep dermis are seen spared, vascular proliferation is seen in subcutis (arrowheads) (A, B) (H.E. x40). Some malformed vessels in the subcutis (B,inset) (H.E. x200).

purple to black verrucous plaques and nodules on the lower extremities [2,3]. Unlike hemangiomas, VVM tends to progress and extend in proportion the child's growth and doesn't spontaneously regress [2,3]. ACN resembles VVM in terms of clinical presentation, behavior and course. ACN may range from a few centimeters to expansive plaques encovering a considerable part of the body most commonly involving the unilateral lower extremity even though neck involvement was also reported as a rare occurrence [2,4]. Since ACN and VVM can not be differentated from each other based on clinical grounds, histopathological examination is the gold standard for the correct diagnosis [2]. Angiokeratoma is characterized histopathologically by dilated, thin-walled vessels in the papillary dermis, whereas orthohyperkeratosis and cavernous vascular spaces encircled by flattened-malformed endothelial cells which may extend to the deeper dermis and subcutaneous tissue, are observed in VVM just like our case's histopathological examination findings revealed [2]. Surgical excision combined with skin grafting, CO2 laser for residual or recurrent thick plaques and argon or pulse dye laser for thin, erythematous patches showed promising results in a study by Yang et al. [5]. In another study, it was shown that the thick- hyperkeratotic parts of VVM best

respond to CO2 laser whereas the dual pulse dye laser-Nd:YAG laser is the treatment of choice for the deeper vascular components [6].

CONCLUSION

All in all, we want to emphasize that VVM is a rare vascular malformation that should be kept in mind as one of the differential diagnoses in patients presenting with unilateral, hyperkeratotic, verrucous vascular papules and plaques.

Author contribution

Study conception and design: EB, BYA, BY, and OG; data collection: EB, BY, and OG; draft manuscript preparation: EB and BYA. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Ethical committee approval was not needed for the present case report.

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Conflict of interest

The authors declare that there is no conflict of interest.

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